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Announcement

THE JOURNAL OF CHRONIC DISEASES

The JOURNAL OF CHRONIC DISEASES begins publication on a monthly basis with this, the January, 1955, issue. It is a new venture in medical literature, which finds its stimulus and reason for being in an awakening medical and public interest in the increasing importance of chronic illness.

The background of this birth of interest and the ramifications of the problems to be faced have been recently and succinctly summarized in the Magnuson report, from which a number of quotations are presently drawn.

On Dec. 29, 1951, the President of the United States appointed a Commission on the Health Needs of the Nation, under the Chairmanship of Dr. Paul B. Magnuson, with fifteen distinguished members. The Commission presented a voluminous report[1] on Dec. 18, 1952, in the course of which much space was devoted to chronic illness and rehabilitation.

As to *chronic illness*, the condensed report contained this partial summary:

"Society is increasingly, though still insufficiently, aware that: (1) chronic illness is a tremendous, but by no means a hopeless, problem, (2) much chronic illness can be prevented, (3) its disabling effects can be minimized or avoided in many instances. A fact about chronic disease that is not so well known is that laboratory tests may disclose its presence much earlier than symptoms.

"The basic characteristic of chronic disease, of course, is its long duration, often necessitating medical care for months or years. Examples are heart disease, high blood pressure, cancer, arthritis and rheumatism, tuberculosis, diabetes (mellitus), blindness, cerebral palsy, poliomyelitis, and multiple sclerosis.* *Chronic illness affects persons of all ages; over one-half of the chronically ill are under 45 years of age, more than three-fourths are between ages 15 and 64.*† As a

*Other examples are accidents, deafness, epilepsy, mental disease, syphilis, and fungus infections.
†Italics throughout this long quotation are ours.

result of medical discoveries of the past few years, many chronic diseases are now largely controllable, e.g., diabetes [mellitus], pernicious anemia, and syphilis. . . .

"Ten years ago almost everyone regarded chronic illness as a hopeless affair. Today that is no longer the case. Emphasis on prevention and on rehabilitation has brought about a change. Ten years ago chronic illness was thought to be a problem of old age; today it is widely recognized as affecting all age groups.

"Ten years ago the physician was considered the single important factor. Today we recognize that, even more than in acute illness, the patient has a tremendously important role to play. The physician is important and so is the nurse and the whole medical team, but the patient himself has to decide that he wants to make an adjustment to his illness and work his way through to rehabilitation.

"Ten years ago most chronic illness was traced to a single diagnosis. Now we know that most chronically ill people have two, three, some even as many as seven or eight causes of disability. Ten years ago the approach was by disease categories—control of tuberculosis, cancer, or heart disease. Now the common denominators in these disease problems are recognized.

"Ten years ago the approach was philosophical and often emotional. Today activity has moved into the methodological stage. *In the literature of the last 3 or 4 years there appears less exhortation for something to be done about chronic illness and more on just what to do and how to do it.* . . .

"Cardiovascular-renal disease and cancer now cause two-thirds of all deaths in the United States. Many chronic diseases, on the other hand, do not take lives directly but cause great disability, both temporary and long-term invalidism, e.g., rheumatism. Altogether it has been estimated that *chronic disease results in half to three-quarters of a billion man-days per year lost from productivity.* Chronic illness also accounts for public expenditures of about $1.5 billion a year for medical and hospital services and about $1.5 billion for cash benefits.

"To the individual family, chronic illness often presents an overwhelming financial problem, in fact wiping out family resources and causing dependency on public funds. Although present prepayment plans afford some protection against acute illness, they usually do not cover the hazards of chronic disease.

"Neglect in caring for persons suffering from chronic disease can no longer be tolerated on either humanitarian or economic grounds. Vigorous action is needed to put to work what is already known about controlling chronic disease and to acquire new methods of control.

"The long-range approach to chronic disease must be preventive. Yet, probably *in no other health field is available knowledge so little applied as in the prevention of chronic disease.* At least 17 chronic diseases are largely controllable and 27 are partially controllable by preventive methods now available. These include both measures which avert the occurrence of disease and those which halt or retard the progression of disease into disability or death.

"Some chronic diseases and impairments can be entirely avoided. Good obstetrical care will minimize the occurrence of cerebral palsy. Wearing protective goggles on certain jobs will prevent blindness. Avoidance of obesity

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will substantially reduce the likelihood of diabetes, hypertensive heart disease, and other chronic diseases. Control of known industrial hazards will lower the incidence of cancer. . . .

"There is, however, a practical [community] way to accomplish a large part of early detection [of chronic illness]—multiple screening. This means the application of a battery of economical, rapidly applied tests to screen out apparently well persons who probably have a disease from those who probably do not. The fact that many chronic diseases develop insidiously to the danger point, the fact that the same individual may have several chronic diseases detectable by laboratory tests, the fact that these tests are most economical when applied on a sizable scale—these facts support the extension of multiple screening, not only in physicians' offices but also in hospitals and health centers. . . .

"General hospitals have gradually had to absorb a large number of the chronically ill without sufficient adjustment of services. Many such patients are still shunted into outmoded 'county homes' and inadequately financed nursing homes where poor care is provided. Public assistance agencies, although not adequately staffed or financially supported to administer medical care programs, have provided an ever increasing amount of care for the chronically sick.

"Organized home care programs have been developed in several localities. These can be a means of bringing high quality medical and related services to patients in their own homes, with more economy and at least as good results as comparable services in a hospital. But adequately organized home services are available in relatively few communities and then only to limited segments of the population.

"The range of services needed for persons disabled by chronic illness include: adequate diagnostic and medical service in a hospital or out-patient department; adequate medical services at home, including the co-ordinated services of a physician-led team of health personnel; rehabilitation services in hospitals, at home and in rehabilitation centers; care in nursing homes; selective job placement; sheltered workshops and day care centers; sheltered domiciliary care.

"The service to chronically ill persons should provide the same fidelity and dignity of care now usually accorded the patient with acute illness. Needs of the chronically ill should be met in plans for general medical care, not in isolated programs. There should be close administrative, professional, and geographical ties between a general hospital and all other facilities and services for the chronically ill, including home care services. Services should be organized so that patients can move easily to and from home, hospital, and nursing home.

"Medical education has only recently increased its emphasis on the early recognition and treatment of chronic disease. In the past, medical and nursing students saw almost exclusively persons who were ill, mostly people ill enough to be in bed. As the medical schools begin to assume responsibility for the health of a group of persons—well, acutely ill, and chronically ill—the attitudes of physicians and nurses will better reflect the proper emphasis on chronic illness.

"WE, THEREFORE, RECOMMEND THAT:

"1. A bold attack be made on chronic disease with emphasis on multiple screening to detect disease early, in physicians' offices, hospitals, industry, schools,

and health centers, promoted by the agency which has effectively pointed the way in preventing communicable diseases—the health department.

"2. Diagnostic and rehabilitation facilities and services be improved and extended.

"3. All communities develop well organized home-care services which will bring to patients in their own homes the specialized care which is now usually available only in hospitals.

"4. Physicians, nurses, and other health personnel receive better training in the skills and attitudes necessary for the proper care of those suffering from chronic diseases.

"5. Field (epidemiologic) research into the causes of chronic illness and administrative research into the most economical and effective methods of caring for those with chronic illness be undertaken."

Of *rehabilitation*, the Commission's summary said:

"Until recently the handicapped was truly the forgotten and neglected man. The condition of these unfortunate individuals was deplored but little or nothing was done about them except for an insufficient amount of charity.

"Now the pressure to do something about this problem is increasing. The very medical advances which have preserved so many lives have also led to an increasing number of disabled persons. Unless restored to usefulness, these people waste their energies and talents, often require public funds for subsistence, and even require assistance of other people in attending to the daily necessities of life.

"Estimates based on the results of surveys conducted in 1949-50 by the Bureau of the Census indicate that 2 million disabled persons in this country could be rehabilitated and placed in employment or in more productive work. Each year an additional 250,000 persons become disabled to the point of needing medical services in order to achieve or improve employability. In 1953, public assistance benefits because of disability will amount to about $500 million. While loss of economic productivity is clearly important, much disability is so severe that it extends to a point requiring other persons to spend time in attending to the personal needs of the disabled. Thousands of persons in the United States are paralyzed as a result of stroke, poliomyelitis, and other conditions. They occupy hospital and nursing home beds and utilize nursing time which could be released in great part if these patients were rehabilitated to the point of self-care, even though not to employment.

"*Disability affects children and the elderly as well as those in the most productive years of life.* It arises from a wide variety of conditions—blindness, heart disease, injuries, multiple sclerosis, and many more. In addition to the tremendous loss of productivity and other economic costs, the cost in individual and family suffering cannot be neglected.

"Rehabilitation is 'the restoration of the handicapped to the fullest physical, mental, social, vocational and economic usefulness of which they are capable.' It requires a total evaluation of the individual from many standpoints and undertaking a program of treatment aimed at maximum recovery. If it is to be fully effective, the idea of 'total care' should pervade all treatment efforts, from the

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time the patient first consults a physician until every possible thing has been accomplished. Rehabilitation, or its failure, actually begins when the physician first sees the injured person or establishes the diagnosis of an illness.

"Hence, primary responsibility rests with the physician who first encounters the disabled person. For greatest accomplishment, there should also be at the disposal of the disabled person, depending upon his particular needs, a wide array of other professional talents—including those of the physical therapist, nurse, occupational therapist, medical social worker, and psychologist. . . . The earlier a patient finds his way into the hands of such a group, the greater the likelihood of rehabilitation.

"Most general hospitals could offer such services, yet a recent survey of general hospitals disclosed that only 65 out of 1,600 replying had organized rehabilitation services and only 18 allocated specific beds to physical medicine and rehabilitation. There is need also for specialized rehabilitation centers, staffed and equipped to serve individuals with severe disability whose conditions require the most highly trained skills. . . .

"The major recent impetus to rehabilitation in the United States came from experiences of World War II. Military and civilian manpower needs focused attention on the tremendous wastage involved in our neglect of the disabled. Advances in surgery, physical medicine, and other techniques made possible the physical restoration of many individuals previously considered hopeless. . . .

"WE, THEREFORE, RECOMMEND THAT:

"1. An increased number of physicians, dentists, nurses, and paramedical personnel be trained in the special techniques of rehabilitation—both through expansion of facilities and through active recruitment of personnel supported by fellowships; and that all health personnel be oriented in the concept of total care of the patient

"2. Development of rehabilitation departments in general hospitals wherever feasible, specialized rehabilitation centers to serve the most difficult cases and to undertake training and research, be encouraged through use of Hill-Burton hospital construction funds and other resources.

"3. The Federal-State vocational rehabilitation program be strengthened and expanded through increased Federal appropriations and State matching funds.

"4. Critical examination be made of present policies in workmen's compensation, disability insurance plans (both governmental and non-governmental), welfare programs, and employment practices with the intent of strengthening those policies which favor rehabilitation and abandoning those which impede it."

The President's Commission attached *special importance to research in the field of chronic illness* in the following words:

"Chronic illness is a field which demands much greater probing. While there has been considerable research on specific aspects of these diseases and some on the development of control measures following the detection of disease, little emphasis has been placed upon longitudinal studies of chronic illness.

These long-term studies of the occurrence of chronic disease in large segments of the population should lead to preventive measures. *We need considerably more information on the natural history of these diseases, the physiological characteristics of individuals who fall prey to them, and the relationship between the individual's mode of life and the occurrence of disease.*

"Scientists must have increased opportunity to observe environmental factors as they affect health and produce illness. We have lagged behind a number of European countries in relating disease to living conditions, to occupations, and to other factors in the environment. We need community laboratories where we can add the skills of biosocial research to those of the biochemical and biophysical sciences. We must seek basic knowledge of occupational factors in cancer, nutrition in heart disease, family life and personality development in mental health, and of housing in total health.

"WE, THEREFORE, RECOMMEND THAT:

"Greater stimulus be given to research on mental illness and chronic illness, with particular emphasis upon research into the relation between the social conditions of life and disease."

* * *

Since the publication of the Report of the Commission on the Health Needs of the Nation in December, 1952, there has been an acceleration of the mobilization of local and national resources to meet the problems of chronic disease. At the local level, over the past twenty-five years, a number of cities, counties, and states had developed research institutes for the study of prolonged sickness and some had established sound programs for the improved treatment of patients in this category. There had been only a few cases where privately endowed institutions had been able to offer exemplary medical care to the chronically ill.

It has taken a long time to give substance to the proposition of one of us (D. S.)[2] that "the basic principle in the care of the patient with long-term illness is that he should be treated with the same fidelity and dignity usually accorded the patient with acute illness. Only within recent years has it become possible to exact this attitude. Hospital facilities for the chronically ill were inadequate because the community conscience had not been sufficiently developed to insist upon satisfactory care of the long-term patient. The chronically ill were often housed in dilapidated ancient buildings. Medical and ancillary assistance were unsatisfactory.

"Some happy changes have come about to dispel this gloomy situation. Hospital authorities have recognized that the long-term patient (the most common type of patient in the over all institutional picture) is more concerned with his environment than the acutely ill individual, who may spend only one or two weeks in the building. Hospitals have been constructed to give the long-term patients pleasant surroundings with a reasonable degree of privacy. Opportunities for recreation and rehabilitation have been emphasized. Improved care by nursing and social service groups has developed in such areas.

"It is likely that the patient with long-term illness will be given better care if the chronic disease pavilion is part of a general hospital organization.

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In this way the integration of the diagnostic and therapeutic facilities of the acute and chronic services will lessen the possibility of improper care of the long-term patient. The quality of medical care will be improved if the hospital for chronic diseases is affiliated with a medical school. The addition of a research unit should attract physicians of high quality. This then leads to a general increase in the over all calibre of care for the individual patient."

The development of an institution for the chronically ill along these lines meets the urgent needs of the patient, the family, and the physician. The comfort thus afforded the sick needs no amplified description. The newer opportunities for providing good care to the long-term patient are immediately evident to the family physician. Participation in these activities enables him to reinvigorate his graduate self-education.

Two recent developments at the Federal level emphasize a direction of medical and legislative thinking. The National Institutes of Health at Bethesda, Maryland, which are largely concerned with laboratory and clinical investigations of long-term diseases, have received an increase in their research budget from $71,218,000 to $81,268,000 (current year). In addition, the Eighty-Third Congress has passed legislation granting $21,000,000 to the states to help build diagnostic and treatment centers especially for individuals with long-term illness, for rehabilitation facilities, and for nursing homes. The Congress further increased funds available for rehabilitation service for the handicapped from 23½ million to 28 million dollars. This represents a perceptive step of assistance in the field of chronic disease.

Until the advent of this JOURNAL, there have been no medical journals specifically devoted to the problems of the chronically ill (excepting that portion of chronic disease in the aged, covered by journals limited to "Geriatrics" or "Gerontology"). *In recognition of the urgent fact that chronic illness affects persons of all ages, this Journal is more interested in its beginnings than in its endings.* Articles dealing with chronic illness are scattered through many medical journals, so many as to prevent even casual inspection by busy doctors. Although the diagnosis and management of chronic disease is largely the function of general practitioners and internists, who spend most of their time with such problems, nevertheless it is hard to name a medical discipline which is not also concerned with similar, if specialized, problems. In recognition of this fact, this JOURNAL will, it is hoped, publish articles dealing with chronic illness as it affects any part of the medical and ancillary professions.

The Editorial Board of the JOURNAL has been chosen because of the wide ramifications of chronic disease. Their names, listed in alphabetic order, their professional affiliations and addresses, and the disciplines which they represent for the Editorial Board are as follows:

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Special attention is directed to the inclusion of representatives of nursing, social service, and the lay public, each of which callings has a major interest in chronic illness.

The new JOURNAL will, it is hoped, include original articles dealing with many phases of chronic illness, including, for example, early diagnosis; prevention; studies of the natural history of such diseases (without which, as a base line, estimates of the value of specific therapeutic measures cannot be made); new methods of treatment; environmental, occupational, and nutritional factors contributing to chronic illness; epidemiology; rehabilitation; the role of practicing physicians, public health officers, and paramedical personnel in chronic illness; evaluation of medical screening procedures and their applicability by doctors generally; institutions and home care; community impact and socio-economic problems; and medical education.

Every effort will be made to publish papers of significant content and to avoid highly abstruse and technical communications which properly belong in more specialized journals. If the Editors and members of the Editorial Board cannot understand a particular paper, they may perhaps correctly assume their readers will be in the same position! On the other hand, emphasis will not be wholly on applied clinical reports; more basic and fundamental investigative laboratory studies will also be acceptable if important to the aim of advancing knowledge of chronic disease.

Each issue will contain one or more review articles dealing with topics of timely interest, and prepared by recognized experts.

An abstract section is deliberately omitted, in part because of the vastness of the field, in part because such sections are of chief value in orienting students of a particular subject and are less appealing to busy doctors, and in part because the field is already adequately covered by specialized abstracting journals.

More valuable than abstracts, in the opinion of the Editorial Board of this JOURNAL, is a strong editorial section, in which important points can be briefly covered, with editorials ranging in length from a single paragraph to several pages.

There has long been a need, in the world's medical literature, for the publication of negative results. Indeed, more than once there has been proposed the establishment of a special Journal of Negative Results, in order to provide space for brief papers, the publication of which may save workers other than the author unnecessary duplication of effort in the same field. A current example of the value of wide dissemination of negative results lies in the chemotherapy of cancer. Many drugs, having shown promise after laboratory screening, fail promptly when applied in man. To make the fact known is to save wasted time and effort on the part of doctors, and perhaps even to save the lives of patients by avoiding a method of treatment already known to be of no value. If papers falling into this category can be attracted in sufficient number—and since they provide negative rather than positive data, they should be brief!—this JOURNAL may in the future establish a Section on Negative Results.

The Editorial Board has wished to avoid too rigid a definition of the content of the JOURNAL, preferring to be guided by the experience of the next few

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years, and by the desires of its readers. The Editor and Associate Editor will welcome comments and suggestions.

Before the publication of this new journal was decided upon, opinions as to its desirability were obtained from about 1,000 physicians, drawn from the membership of the foremost medical societies of internal medicine, from members of university faculties, from public health officers, and other doctors especially concerned with chronic illness. The majority were enthusiastically favorable, on the grounds of the growing importance of chronic illness to the community in general and to doctors in particular, and of the desirability of concentrating scientific data concerning it under the covers of a single journal devoted wholly to its problems.

With this preliminary approbation, the JOURNAL OF CHRONIC DISEASES makes its bow.

JOSEPH EARLE MOORE, Editor
DAVID SEEGAL, Associate Editor

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Original Communications

DETERMINATION OF PROGNOSIS IN CHRONIC DISEASE, ILLUSTRATED BY SYSTEMIC LUPUS ERYTHEMATOSUS

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INTRODUCTION

THE word "chronic" has developed a number of meanings, one being "continuing for a long period of time" and another "constant." But that which continues for a long time rarely remains constant, except in the fact that it continues. In chronic illness, variability rather than constancy is usual, not only with regard to different patients, but also in the course of a single patient. Time is available during a chronic condition to bring to bear the variety of physiologic and environmental changes which produce diversity. The disease may exhibit varying periods of activity or quiescence and, even when it runs an unremitting course, wide differences in rates of progression. Concurrently, the patient himself gets older and has other diseases and experiences which change him physiologically.

These factors complicate enormously the assessment of the biologic changes associated with the disease itself and the evaluation of prognosis. Ideally such an evaluation starts with a survey of the general population to detect the cases from their subtle beginnings and to study the subsequent life experience of the affected and nonaffected persons. Such studies are admittedly difficult and costly. For these reasons, as well as the fact that attention has been concentrated on the simpler and more urgent problems of acute disease, our present knowledge of chronic disease processes, or indeed of normal aging, is rudimentary. Community studies have been recently initiated in which detection of incipient cases of heart disease and diabetes, for example, has been accompanied by provision for follow-up of these cases and of controls free of these diseases. This type of study may lead to prognosis in the fullest sense of the term.

Prognosis for a chronic disease derived, not from cases discovered in the population, but from cases presenting themselves to a physician or clinic may produce a very different picture. When the patients are first seen they will

differ greatly in the length of time they have had the disease. Moreover, these cases may not be representative of those with similar times of onset since some of these will have died, either from the disease or other causes, and others will be alive but not among those presenting themselves to the clinic, for a variety of reasons, including not being sick enough. To what extent the experience of the self-chosen patients who are observed resembles that of the unobserved patients is not known but will depend on the availability of preventive, diagnostic, and other medical services, as well as many other factors in the community. Prognosis based on the follow-up of such patients must therefore be interpreted with caution as representing the natural history of disease.

This raises the question as to whether these figures have any real merit. It seems to us that they have two purposes. First, they may be helpful to the specific clinic in evaluating its own experience with reference to management of the patients. Second, the comparison of results from different clinics may furnish leads with regard to important issues in the natural history of the disease which are basic to the planning of a more comprehensive study on a population framework; that is, they are pilot studies for more complete epidemiologic studies.

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For either of these purposes, the nature of the cases included in the particular study must be explicitly defined and, in addition, the analysis of the follow-up data must be sound. The large number of papers in the medical literature which are unsatisfactory in these respects suggests that the problems and methods around both of these issues can bear restatement. The purpose of this paper is to consider these questions, present specific methodology for dealing with the analysis, and discuss the interpretation which follows from it.

Much of the discussion and explanation of methods will center around a concrete illustration, survivorship in systemic lupus erythematosus (SLE), in part because of the increasing interest in this disease and more especially because the issues to be examined are more easily explained around a specific example than in generalized terms. Elsewhere[1] we have given a critical review of the publications on prognosis in this disease and an abstract of the results of our own analysis. Here we are explaining the methodology by which these results were obtained and discussing the problems of definition and interpretation which SLE shares with other chronic diseases.

The details of procedure are given in an appendix section on "Calculation of a Life Table" rather than in the text so that the features of follow-up observations and the pitfalls to avoid in analysis and interpretation of the data might be considered by the reader apart from specific calculation.

FEATURES OF DATA FROM LONG-TIME STUDIES

There are two characteristics of long-time follow-up observations that complicate the analysis of survivorship (or of progression to some end point other than death). First, people come to observation at different stages and after different durations of the disease, and therefore present a problem as to the initial point from which prognosis should be estimated. Second, they have

been followed for variable lengths of time because of different calendar times of entry and loss from observation; for these same reasons they have not all been followed to death (or to the end point selected). Misunderstanding with regard to the handling of these characteristics in developing survivorship rates is largely responsible for the gross errors and contradictions in the literature.

The Starting Point.—If in describing prognosis we say that x per cent of the patients survive one year, the statement is meaningless unless we say one year from what. The measurement of prognosis must be from some defined point. The starting point from which the prognostic figure is constructed may be a date concerned with the management of the case such as first observation, diagnosis, or date of first treatment, or it may be a specific landmark in the course of the disease reached after the patient comes under observation. The temptation is often great to strive for the natural history of the disease by predating the starting point to onset of symptoms or some other point prior to the patient's coming under observation. Unfortunately this almost invariably gives fictitious results. In the first place, there is great uncertainty in dating vague and often subjective first symptoms. This, however, is not the only objection to predating the starting point, for even if we could get an objective definition of onset we would still be faced with the fact that the patients coming to observation are selected through the omission of patients having a similar onset who did not come to the clinic. Those failing to come are so likely to have had a different course of the disease that our observed experience cannot be assumed to be representative of cases from onset.

To illustrate the possible distortion involved in predating the starting point for prognosis, consider the measurement of the survivorship of newborn infants to age 1 year. The sound and standard procedure is to follow infants from birth to age 1 to determine the proportion surviving. Suppose we are running a vaccination clinic and have a group of infants whom we see for the first time when they are presented for vaccination. Since we can get the date of birth of each we can follow each to his first birthday to see the proportion who survive to that date. But if we gave this as the proportion of newborn infants who survived to their first birthday we would greatly overestimate survival in general because of the selection. This example seems extreme because our knowledge of infant mortality is sufficiently complete to make the absurdity of the result obvious. However, the procedure is logically identical to stating prognosis for a disease from onset on the basis of predating the patient's experience. The fact that the size of the error for a particular disease is unknown, as is usually the situation, is no assurance that it is small, and predating is therefore to be avoided.

Variable Length of Follow-Up.—The variation in length of observation comes about in part because some patients die and this occurs at various times; in part, because some patients will inevitably be lost to observation after different periods for causes other than death; and finally, because the patients have entered the series at different times. This accrual of cases with time means that at any moment when we choose to take stock of our experience, some persons, still alive, will have been followed for only a few days or weeks, some perhaps for

many years. The analytic problem is that of assembling the experience contained in these variable lengths of time to get meaningful figures for prognosis.

The influence of this variable follow-up on the determination of prognosis is easily overlooked. Two erroneous procedures which appear regularly in the medical literature will be cited to point up this issue and to indicate the need for a different approach. One of these tries to state prognosis in terms of the percentage surviving five years, say, from diagnosis, by adopting the direct approach of dividing the number of those known to be alive at the end of five years by the number of cases diagnosed. But we do not know, and have not included, all the five-year survivors among those diagnosed. First, we do not know how many survivors there will be among those lost to observation in the first five years after diagnosis. This calculation assumes that all such lost persons die before the end of five years. Second, we do not know the five-year survivors among those cases diagnosed within the last five calendar years and still alive, because their fifth anniversary has not yet arrived. This calculation assumes that they all die before the fifth anniversary. This approach is certain to underestimate survivorship.

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A second erroneous method seeks the average duration of life after diagnosis and tries to get this by averaging the interval from diagnosis to death of those who have died, up to the time of the analysis. Those still alive do not enter the calculation at all, since their interval to death is unknown. This almost inevitably gives an erroneously low estimate of the average duration of life since the deaths are commonly loaded with those who die promptly and are deficient in the long-lived.

These two methods are reviewed, not only because they are frequently used, but because they characteristically lead to errors of considerable magnitude. They can in no sense be considered "approximate but acceptable" procedures.

The problem we face in these studies is an old one with the insurance companies since they deal with an exactly analogous situation. When an insurance company undertakes an analysis of its experience at any time, it must cope with observations on persons who have taken out insurance at various dates and ages, on persons holding their policies for a time and then dropping them, and on persons dying after different durations of insurance. Their lapsed policies are the "lost" cases of the chronic disease study. Their "policy age" is our "years after initial point of the study." Thus, their solution for getting estimates of risk of dying or chances of survival, known as the "life table," is applicable to our problem. The life table gives the proportion surviving to various points of time from the starting point selected for the study, and other indices which can be derived from these proportions.

While a number of different methods for deriving a life table are known (see, for example, references 2 and 3), all of them take explicit account in one way or another of the issues mentioned previously, namely:

Definition of the starting point;

Length of follow-up for:

those lost to observation,

those still alive and under study, and

those who have died.

In considering the use of life table methods it should be emphasized that the statistical manipulation for handling "lost" cases involves a correction for the length of follow-up but not for the fact that the lost cases may differ in one or more characteristics from those still under study. If a substantial proportion of the cases is lost to follow-up and these are unrepresentative of those entering the study, no statistical procedure whatever will give reliable estimates of prognosis, and none should be attempted.

DEFINITION OF CASES

The utility of prognosis figures either to the staff of the institution from which the cases come or to medical scientists elsewhere is directly dependent upon the specificity with which the cases are defined, as to both inclusion and exclusion. This has been fully discussed and illustrated by Densen[4] in a paper devoted to this issue alone.

The complexity of most chronic diseases means that definitions which satisfy the investigator himself are not easy to delineate, even when he is setting up these definitions as part of the advance planning of a study. Far greater problems arise when the prognosis is to be made on the basis of cases diagnosed at the institution in the past. Hospital histories have glaring deficiences because of incompleteness of records, unstated criteria, variability in nomenclature, change in awareness and interest in the disease, and changes in diagnostic techniques. These difficulties are encountered in every retrospective study based on hospital histories and had to be faced in attempting to determine prognosis in systemic lupus erythematosus.

The study was based on 99 cases diagnosed at The Johns Hopkins Hospital, either in the inpatient or outpatient services, during the years 1949 through 1953. There were three additional cases observed during these years. Two of these cases were diagnosed post mortem and thus have no relevance to a prognosis analysis, and one could not be followed. Initially, we explored the possibility of studying survivorship in cases diagnosed prior to 1949 but they were omitted because in that year awareness of the disease sharply increased, largely from the development of the L. E. test and the therapeutic use of ACTH or cortisone.

The assembling of the cases and the efforts to insure their completeness presented a number of problems associated with the multiplicity of services and records in a large hospital. Our list comes from several sources: the files of the hematology laboratory where the L. E. tests were recorded, the records of the group interested in the treatment of this disease with hormone therapy, the patient files of the medical investigators interested in SLE, and, finally, the patients listed in the records of the statistical department of the hospital. The list from the statistical department was supposed to be complete through 1951 but a check against that from the other sources showed a substantial number of missing cases due to incorrect diagnoses assigned by the hospital physicians or to coding errors by the statistical clerks, which emphasized the need for exploring the other files.

No single diagnostic criterion for SLE is available and we have found it difficult to arrive at a satisfactory set of criteria. Initially, we were attracted to the concept that all cases must be "proven" by finding L. E. cells and/or pathologic changes. However, there are several objections. We have seen cases: (1) in whom L. E. cells were not found although the clinical diagnosis was apparent and lupus was found at post-mortem examination; (2) with negative L. E. cell test and a positive biopsy; (3) with unequivocally active lupus on clinical grounds in whom L. E. cells were not found until after repeated searching over months or years; and (4) with fulminating lupus and only minor pathologic changes after meticulous search at post-mortem. In general, examination of biopsy material has not been fruitful and the evidence at post-mortem examination has not always been clear-cut. Consequently, we have elected to include cases in whom the diagnosis was not confirmed by the presence of L. E. cells or pathologic evidence but in whom the diagnosis was agreed upon by several observers and in whom there were at least seven, and at times as many as fourteen, manifestations of the disease.

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Table I lists the number of patients in whom the diagnosis was clinically apparent and those in whom it was clinically in doubt, as well as the number in whom the diagnosis was either confirmed or established by L. E. cells or biopsy or autopsy material. It should be noted that no cases can be included in this type of prognosis study which were diagnosed solely by autopsy.

TABLE I. DIAGNOSTIC CRITERIA IN NINETY-NINE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS, THE JOHNS HOPKINS HOSPITAL, 1949-1953

CONFIRMATORY EVIDENCE*	NUMBER OF PATIENTS		
	CLINICALLY APPARENT	CLINICALLY DOUBTFUL	TOTAL
L.E. cells positive	44	23	67
L.E. cells and biopsy positive	2	6	8
Biopsy positive	5	2	7
Autopsy positive	5		5
Unconfirmed†	12		12
Total	68	31	99

*The classes are mutually exclusive.
†Neither L.E. cell test nor biopsy was performed in four.

We wish to emphasize again that in follow-up studies on other chronic diseases we have found corresponding problems in definitions and criteria. We have devoted considerable space to the question here because it is characteristic of the general problem and not unique to lupus.

CHARACTERISTICS OF CASES

Once the cases to be included in the study have been defined, their characteristics must be studied for a number of variables. The interpretation of the

findings in any analysis of survivorship will depend upon the make-up of the group of patients as to those attributes for which the general population shows marked differences in the rate of dying. The description of the cases should as a minimum include age, race, and sex distributions. Of these, age distribution is especially important, and survivorship must be judged against that expected for general people of these ages followed over the same observation period as that for the patients under study.

In addition, the cases should be described for those features believed to be important in the biology of the disease and its management. These will, of course, differ with the disease and with our knowledge of it. A great deal of attention has been given to the development of classifications of stages of syphilis and tuberculosis, less in many other chronic diseases. When these classifications can be made with some precision they are valuable in characterizing the material under study and may contribute to the prognostic analysis in a variety of ways. On the other hand, when the classifications are poorly defined, and used differently by different investigators, as they are in SLE, they may actually be misleading.

In the description of the cases, we are hampered not only by our limited knowledge as to relevant classifications but also by the difficulty of assessing the effect of the numerous factors influencing the type of patient population present at a given institution. A staff group having a special interest in a particular disease is likely to observe the disease with more than usual frequency, to transmit their interest and awareness to others in the medical environment, and to attract patients from a broad area. Developing knowledge will alter the interpretation of criteria and the treatment of patients. All such factors produce differences in patient populations in different institutions and changes in these populations with time.

For our illustration of SLE the patients are described for age, sex, and race, as characteristics relevant to general population comparisons. The estimated duration of symptoms is the only factor considered here relating to the biology of the disease. As to the management of the cases, it is sufficient to state here that 24 of the 99 had no treatment, and the remaining 75 received some form of hormone therapy, differing greatly in type of hormone, route of administration, dosage, and duration of therapy.

TABLE II. CASES OF SYSTEMIC LUPUS ERYTHEMATOSUS DIAGNOSED AT THE JOHNS HOPKINS HOSPITAL, 1949-1953, BY SEX AND RACE

RACE	SEX		TOTAL
	MALE	FEMALE	
White	12	61	73
Negro	1	25	26
Total	13	86	99

The sex and race distributions are shown in Table II. Approximately 75 per cent of the patients are white, and 85 per cent, female. The color distribution is essentially that of the hospital population but the preponderance of

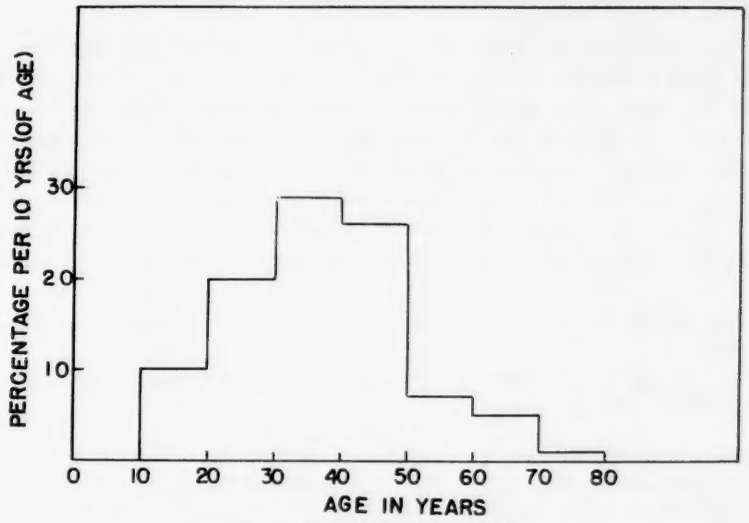

Fig. 1.—Ages at diagnosis of SLE.

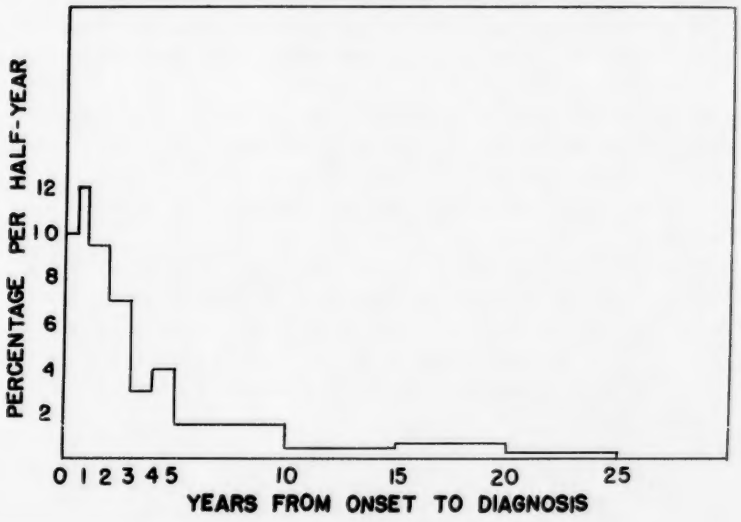

Fig. 2.—Intervals from onset to diagnosis of SLE.

females is not. The lack of knowledge of the population from which these patients arise and uncertainty about their self-selection make it impossible to interpret these figures as indicating relative incidence of the disease for different

classes in the population. The figures will be used, however, in arriving at an estimation of normal mortality to be expected in these patients.

The distribution of ages at diagnosis is shown in Fig. 1. The ages range from 13 to 71 years, the median being 36.6 years. The sex and color subgroups show no significant difference in age distribution.

On the basis of their histories, an attempt was made to assign a date to the onset of symptoms, not, of course, to use onset as the starting point, but to describe the cases under study. In cases of uncertainty of symptoms we have selected the more definite and recent ones. The duration of time between the estimated onset and the date of diagnosis varied from less than one month to thirty-five years, but the distribution is piled up toward the short intervals as shown in Fig. 2. The great variation in this graph points to the fact that SLE may appear suddenly or may develop insidiously so that a long period may elapse before the disease is recognized. In this variation, SLE exhibits one of the traits that make the chronic disease problem so difficult to assess in its prognosis.

The bearing of these descriptive facts on the conclusions from the analysis will be considered later.

ANALYSIS OF DATA

The analysis of long-time follow-up observations is necessarily in terms of a life table or its equivalent. This type of analysis is applicable even when some end point other than death is used, so that our discussion in terms of death or survivorship may be thought of as only one application of the method. Various indices of prognosis are available from a life table but the one that is most readily interpreted is probably the proportion surviving to various times beyond the starting position.

For the cases of lupus, an estimate is made of the percentage of patients surviving to various points in time *after diagnosis*, which is taken as the starting point. We will now consider the approach to the derivation, which is carried through in detail in the Appendix, and then return to a consideration of the interpretation.

The relevant facts, for each of the 99 patients, required for the determination of survivorship are date of diagnosis, date of latest observation, and status at latest observation, that is, whether living or dead. These are given in Appendix Table A. To illustrate the individual patterns of experience, the following cases are selected from this table and shown graphically in Fig. 3:

CASE NUMBER	DATE OF DIAGNOSIS	DATE OF LATEST OBSERVATION OR DEATH	STATUS AT LATEST OBSERVATION
3	3/1949	12/1953	Living
5	3/1949	9/1953	Dead
15	11/1949	6/1950	Dead
36	10/1950	11/1950	Living (lost)
45	5/1951	1/1954	Living
46	5/1951	6/1953	Dead
92	9/1953	2/1954	Living

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In Fig. 3*a* each line represents a patient, the line starting at the date of diagnosis and continuing to the latest observation, so that the length of line shows the duration of follow-up. The three open-ended lines (Cases 3, 45, and 92) show cases that are still being followed, in that the patients were alive when last seen, and are presumed to be available for later examination. On the other hand, Case 36 (closed with a single line) although alive when last seen has not been located for subsequent examination and is counted as a lost case. She therefore contributed only one month of observation to the study. The remaining three cases, closed with a double line, died at times after diagnosis that were, respectively, 4½ years, 7 months, and 2 1/12 years.

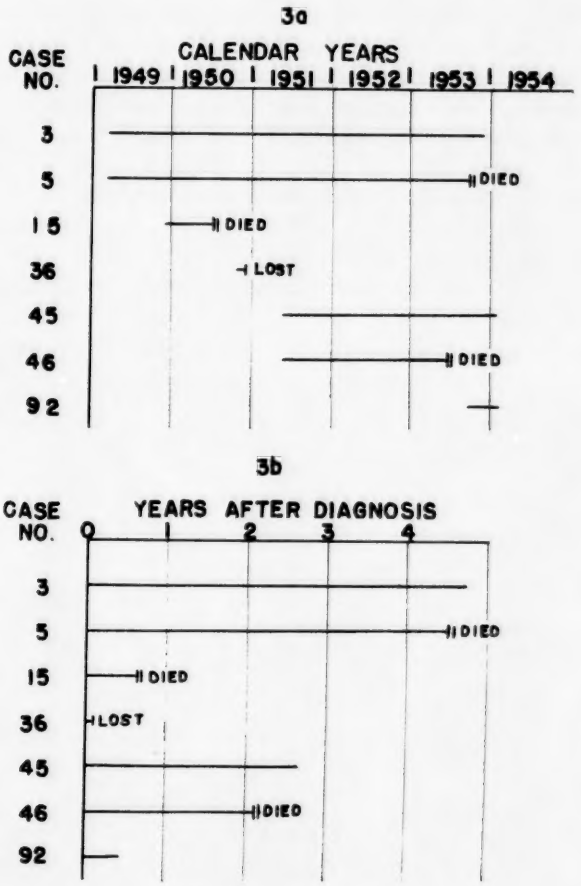

Fig. 3.—Sample of patterns of observation.

Since date of diagnosis is taken as time 0, it is convenient to reconsider this diagram on the basis of follow-up years rather than calendar time. This is shown in Fig. 3*b*, where the lines are slid over to start at an origin defined as time

of diagnosis, and the annual divisions represent anniversaries after diagnosis. This diagram among other things shows up the difficulty of direct computation of percentages surviving. For example, if the proportion surviving two years is desired, it is seen that Cases 3, 5, 45, and 46 are known to have survived, since their lines cross the second anniversary line; Case 15 is known to have died prior to this; for Cases 36 and 92 the answer is unknown, because of loss from observation for Case 36 and only because of recency of diagnosis for Case 92. In spite of the fact that survivorship to two years is unknown for such patients, the fact that they were alive at last observation yields pertinent information and they should not be discarded from the analysis.

The problem of analyzing survivorship is that of utilizing the information furnished by each individual for the entire time that he was under observation. The patterns of the 99 individuals in this study, typified by the 7 cases just considered, show that 30 were followed to death within the first four years after diagnosis, 65 were last observed sometime within these first four years but were alive at this time, and 4 were observed to reach their fourth anniversary. The tabulation of the times at which these deaths and latest living observations occurred is the basic tabulation from which the probability of survival is computed. This is given in Table B in the Appendix. The procedure by which it leads to survival rates accompanies it.

The results of this calculation are shown in Table III and presented graphically in Fig. 4. The horizontal scale, x, gives years after diagnosis, and the vertical scale, the percentage of the diagnosed patients estimated to survive x years.

TABLE III. ESTIMATED SURVIVORSHIP AFTER DIAGNOSIS FOR NINETY-NINE PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS, DIAGNOSED AT THE JOHNS HOPKINS HOSPITAL, 1949-1953

YEARS AFTER DIAGNOSIS (x)	PERCENTAGE SURVIVING x YEARS (P_x)
0	100
0.25	87
0.50	85
0.75	82
1.00	78
2.00	67
3.00	62
4.00	51

Death of patients is rapid within the first quarter after diagnosis and then there is a slowing up of the rate. A careful study of the rates shows that after the first quarter year, the rate of death of the survivors is nearly constant, such that about 10 per cent of the persons alive at any time will die within the following year. About one-half the patients are estimated to survive four years after diagnosis. This estimate has considerable uncertainty due to small numbers of cases, especially in the later periods, and no attempt was made to carry the calculation beyond this time.

It may help in understanding this survivorship curve to point out the enormous difference between the percentage estimated to survive four years after diagnosis and the percentage under observation four years after diagnosis. We estimate that 51 per cent survive four years, yet only 4 per cent (4 of the 99) have been observed four years. The reason for this discrepancy is that 65 living persons had their latest observation at some time prior to their fourth anniversary mainly because they entered the study within the last four years. The life table predicts that 51 per cent of the 99 patients (or 51 patients) will survive four years. Therefore, in addition to the 4 known to survive four years, 47 of the 65 are expected to survive this long when sufficient calendar time has passed to carry all of these patients to their fourth anniversary. Conversely, 48 deaths are expected, and thus 18 deaths are predicted in addition to the 30 so far observed.

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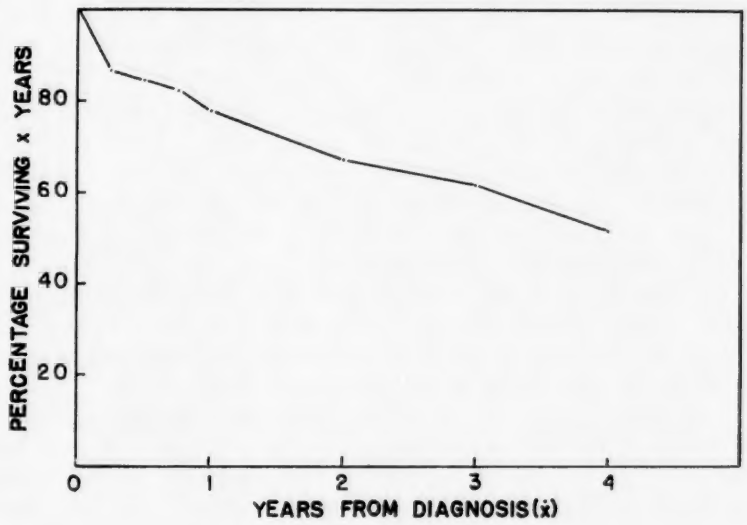

Fig. 4.—Survivorship after diagnosis of SLE.

Since the life table is based on the total experience of the patients for as long as they were followed, the prediction for these patients subsequent to their last observation necessarily comes from the experience of those diagnosed earlier in calendar time and hence capable of being followed into the later periods. Such experience must be continually watched for changes in the character of the patients or effects of treatment which might alter the prognosis.

INTERPRETATION

The interpretation of any prognosis estimate will depend upon the specific findings of the study in the light of the number of cases, and the character of cases on which it is based, as well as on such knowledge of the disease process

as is available. It should, if possible, relate the study's results to survivorship in the general population.

For our illustrative purposes we shall consider for lupus the influence of number of cases, selection of cases, and normal survivorship on the conclusions.

If the estimates of survivorship at successive times had been reached by actually following all ninety-nine patients to death or to the xth anniversary, we could make use of the well-known formula for the standard error of a percentage to determine the standard error of the survivorship estimate at any stated time. This is

$$SE_{P_x} = \sqrt{\frac{P_x(100 - P_x)}{N}} \quad (1)$$

where P_x is the percentage surviving x years and N is the starting number, in this case 99. For the fourth anniversary, for example, the standard error of the 51 per cent survivorship rate, if all 99 had been followed this far, or to prior death, would have been $SE_{P_4} = \sqrt{\frac{51\ (49)}{99}}$ or 5.0 per cent. However, 65 patients were withdrawn from observation along the way, and the effect of this is to increase the uncertainty of the estimate (and therefore increase the standard error) due to the dwindling number of cases on which it is based. The value of the standard error for our illustration is raised to 8.5 per cent when the reduced size of sample is taken into account. There is thus a large uncertainty about the four-year estimate, for if we use the conventional ± 2 (SE) limits of uncertainty, we could say only that the four-year survival rate is estimated to be between 34 per cent and 68 per cent, that is 51 per cent ± 2 (8.5 per cent). For the earlier x positions, such as 1 or 2 years, where the numbers are less drastically reduced, there is greater precision to the estimated survivorship.

It is beyond the scope of this paper to consider the development of the standard error of the estimate based on a diminishing size of sample. The formula used to derive the 8.5 per cent quoted previously (see Appendix) was given by Greenwood[5] and rederived by Irwin.[6] The investigator may, however, get some notion as to the caution necessary against accepting too literally an estimate based on scanty data by recognizing that the readily applied formula (1) gives a *minimum* value and that the effect of a diminishing sample is to increase the standard error appreciably. This diminishing size of sample cannot be avoided if we make full use of our information because the most recently diagnosed cases, of necessity, have been followed only a short time. Every effort, however, should be made against any additional depreciation of the experience, and the "lost" cases should therefore be kept to a minimum.

The relationship of type of case to prognosis is best studied by deriving separate life tables for the subgroups of cases as to age, sex, color, stage of disease, and other factors which may be important. The limiting factor on this approach is the size of the experience. This may be so small that few, if any, subgroups of patients may be analyzed separately.

For our illustration life tables were set up for patients under and over 40 years of age at diagnosis, and no significant difference in prognosis was found.

However, when the cases were separated with respect to the length of time from onset to diagnosis, a difference was found which involves some interesting points in interpretation. Again two broad classes were made, namely, under and over 2 years. The results are presented in Fig. 5. The mortality in the first few months after diagnosis is high and strikingly similar for these two groups and suggests that regardless of duration of illness a substantial number of patients either first appear for diagnosis or are first successfully diagnosed in the terminal stages of the disease. For those who survive the first year following diagnosis, there is a significant difference in prognosis, although the size of the difference is not well established because of the small numbers of patients in each group. This change from similar curves in the first year to dissimilar ones thereafter points to the strength of the continuous survivorship curve as a description of prognosis in contrast to a single point such as the frequently used "five-year survivorship." Any such single value is limited in its portrayal of the full course of events.

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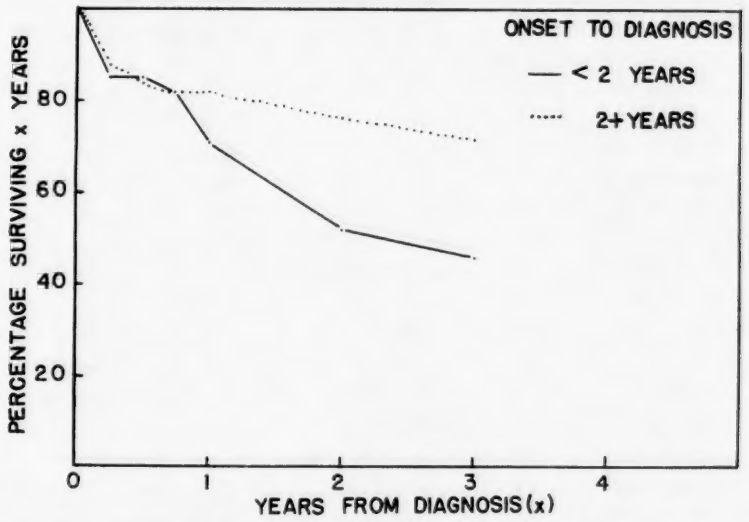

Fig. 5.—Survivorship after diagnosis of SLE by interval from onset to diagnosis.

The direction of the difference also raises an important point in interpretation, for those who were diagnosed shortly after the appearance of symptoms had the less favorable prognosis after diagnosis. The danger of jumping to a cause and effect explanation here is probably avoided because it is rather unattractive to conclude that medical attention achieved early in the course of the disease hastens death. A more appealing explanation is associated with the self-selection of cases considered earlier. Those cases with serious enough symptoms to bring the patient to the doctor early in the course of the disease may well be the type that progress more rapidly.

A cause and effect explanation for a difference that came out in the other direction would be just as dangerous. When cases with an early diagnosis

show a more favorable prognosis it is tempting to attribute this to the advantage of early medical treatment, but this explanation must be eyed just as critically as it is in our case, for patients who seek medical attention when they first notice symptoms may have economic and other advantages which affect prognosis favorably, irrespective of the medical care itself.

One of the most vital issues for the clinician is the assessment of the effect of a new therapy, such as the hormone treatment for lupus, on the prognosis of the disease. This involves the comparison of prognosis in treated and untreated patients, but the source of the two series of patients is critical. The comparison of a currently treated series with an untreated series of a prior era is beclouded with all the time changes in type of patients diagnosed and uncertainties of criteria, mentioned earlier. The force of this has been clearly demonstrated in a study of cases of cardiovascular syphilis at several clinics.[7] Moreover, the comparison between simultaneously treated and untreated cases will be equally erroneous when the decision to treat rests on clinical indications. Consequently, in order to assess the value of any specific therapy, it is necessary to have a planned study having some sort of random assignment of patients to the treated and untreated groups. Recent papers on the nature and value of the clinical trial for such evaluation[8,9] emphasize the generality of this statement, especially for as complex a situation as we face in chronic disease.

The real opportunity to carry out such controlled studies appears when a new treatment is first introduced.[10] It becomes difficult, if not impossible, to set up such a study once the clinicians and patients have developed impressions, however unfounded they may be, as to the merit of the therapy.

The statement that the value of a therapy has not been assessed is not equivalent to saying that the therapy has no effect. The treatment given is therefore an essential part of the description of the cases. In our series, the fact that 75 per cent of the patients were given hormone treatment is as much a part of case description as the diagnostic criteria, and may have had a real, although as yet unevaluated, influence on the survivorship curve.

The interpretation of survivorship figures in the light of the general death rate in the population is best approached through calculation of life tables for subgroups of the cases as to age, sex, and color, and a comparison of these survivorship curves with those available for the population groups with these same characteristics. To do this calls for a very large clinic experience. In the usual situation, where the numbers of patients are small, some other approach has to be used.

One such approach is to determine, by a process of adjustment, the percentage of persons who would be expected to be alive x years later in a population having the same distribution of persons as to age, sex, and color as our group of patients. This procedure was applied to the ninety-nine patients in our series, to compare the four-year survival rate with that expected according to the 1951 life tables in the United States.[11] The cases were tabulated as to sex and color, and each of these four groups was distributed in five-year age groups. For each of these classes, the expected number of deaths within the following four years was estimated from the United States life table for this specific group.

The estimated survivorship so computed was approximately 97 per cent, compared with the observed 51 per cent. This comparison, made with due regard to the sampling error on the observed value, gives some measure of the excess risk for the patients with SLE. Smaller differences between the disease group and the general population would be expected if we were dealing with a chronic disease heavily concentrated in the old-age group.

The comparison of follow-up results for patients in a specific clinic with those in other clinics, as that experience is reported in the literature at the present time, is usually very difficult, if not impossible. The reason for this is that the results have commonly been presented with an inadequate description of the cases and analyzed by diverse and erroneous methods. The purpose of this paper is to explore the issues that must be considered and the type of method which is necessary if we are to build up a literature in chronic disease which will allow of such comparisons.

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Appendix

Raw Data and Calculation of Life Table

The method of computing the results quoted in the text is described here for the survivorship of all cases, irrespective of age, sex, color, or duration of symptoms. Table A gives the data for each patient individually. The essential facts required from this table for the construction of the life table are time from diagnosis to death for those who died and time from diagnosis to latest observation for those alive at this time. The tabulation of the raw data as to these items is given in the first four columns of Table B, and the calculation in the remaining three columns. The explanation of this table follows.

Column 1.—x is time in years from date of diagnosis. The numbers refer to exact points on the time scale, not to intervals, e.g., "2" means the second anniversary from diagnosis.

Column 2.—O_x is the number still under observation at the successive x positions, not in the sense that this number was actually seen on that day, but that they were followed to this time or beyond. For example, O_2 is 29 persons followed beyond their second anniversary and includes Cases 3, 5, 45, and 46 illustrated in the text. O_0 is 99, the total number diagnosed, and the successive values are obtained by subtraction of those withdrawn from observation and those dying, given in columns 3 and 4.

Column 3.—${}_nw_x$ (withdrawals) means the number alive when last seen in the interval beginning with the xth anniversary and ending with the $(x + n)$ th. The double subscript is necessary to define which interval we are considering and its length. In our stated intervals in this table, n is 0.25 year for the first four intervals, and 1 year thereafter. For example, ${}_1w_2$ is 9 living persons (including Case 45 cited in the text) among the 29 followed to the 2nd anniversary who were not followed to the 3rd. The term "withdrawal" refers to the fact that these people contribute nothing to the experience presently being analyzed beyond the point when they were last seen. It does not mean however that they are lost to follow-up, although some of them may have been. For most of them, the recency of their diagnosis determined the position when they were withdrawn from observation, and if the same analysis were to be made one year from now, those surviving would be withdrawn from observation in the interval 3 to 4 years after diagnosis.

Column 4.—${}_nd_x$ gives the number of observed deaths in the interval x to $x + n$, e.g., ${}_1d_2$ is 2 observed deaths in the year 2 to 3 (one of whom is Case 46 of the text), among the 29 persons followed to the 2nd anniversary. It should be noted that the remaining 27 do not necessarily survive this year since the 9 withdrawals were followed only partway through this year and their 3rd anniversary status is as yet unknown.

TABLE A. OBSERVATIONS ON THE INDIVIDUAL PATIENTS WITH SLE, DIAGNOSED AT THE JOHNS HOPKINS HOSPITAL, 1949-1953

CASE NO.	SEX	RACE	AGE AT DIAGNOSIS (YR.)	ONSET TO DIAGNOSIS		DATE OF DIAGNOSIS		LATEST OBSERVATION		
								DATE		STATUS (LIVING OR DEAD)
				YR.	MO.	MO.	YR.	MO.	YR.	
1	F	N	26	3	11	2	49	11	49	L
2	F	N	28	2	9	3	49	4	49	D
3	F	N	35	5	5	3	49	12	53	L
4	F	W	21	2	5	3	49	6	52	D
5	F	W	35	25		3	49	9	53	D
6	F	N	31	2	7	4	49	5	49	D
7	M	W	47		6	5	49	1	54	L
8	F	N	30	17		6	49	6	49	D
9	M	W	33		11	7	49	5	53	L
10	F	W	62		8	8	49	8	50	D
11	F	W	43	1	4	8	49	1	54	L
12	M	W	37	1	6	9	49	8	50	D
13	F	W	60	2	7	10	49	1	50	D
14	F	W	14	3		11	49	12	49	D
15	F	W	21	2	11	11	49	6	50	D
16	F	W	47	1	6	11	49	1	50	D
17	M	W	36	8		1	50	5	53	L
18	F	W	30	3		1	50	10	53	L
19	F	W	18	5	1	2	50	12	53	L
20	F	W	40	2	7	2	50	2	53	L
21	F	N	19		1	3	50	11	50	D
22	F	W	37		1	3	50	6	53	L
23	M	N	50	1	10	5	50	9	53	L
24	F	W	62	8	11	5	50	5	50	D
25	F	W	30	6		5	50	6	51	L
26	F	W	32	6		5	50	1	54	L
27	F	W	52		6	7	50	8	52	D
28	M	W	22		10	7	50	7	50	D
29	F	W	29	1	2	7	50	3	53	L
30	F	W	21	1	3	7	50	11	53	L
31	F	W	29	7	7	7	50	11	53	L
32	F	W	71	4		8	50	10	53	D
33	F	N	27		11	10	50	7	52	D
34	F	W	61	35		10	50	2	54	L
35	M	W	39	10		10	50	8	52	D
36	F	W	19	2		10	50	11	50	L
37	F	W	24	13	1	11	50	7	53	D
38	F	W	38	4	7	11	50	12	53	L
39	F	W	33	6	7	11	50	11	51	D
40	F	N	39	1	6	12	50	1	51	D
41	M	W	64		9	2	51	3	51	D
42	F	W	18		7	3	51	8	52	D
43	F	N	44	5		4	51	1	54	L
44	F	W	40	7	10	4	51	7	51	D
45	F	N	37	7		5	51	1	54	L
46	M	W	23	5	6	5	51	6	53	D
47	M	W	57		5	6	51	5	53	L
48	M	W	51	1	5	6	51	1	54	L
49	F	W	Unknown	2		6	51	2	54	L
50	F	W	45	6	11	6	51	7	53	L

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TABLE A. OBSERVATIONS ON THE INDIVIDUAL PATIENTS WITH SLE, DIAGNOSED AT THE JOHNS HOPKINS HOSPITAL, 1949-1953 (CONT'D)

CASE NO.	SEX	RACE	AGE AT DIAGNOSIS (YR.)	ONSET TO DIAGNOSIS		DATE OF DIAGNOSIS		LATEST OBSERVATION		
								DATE		STATUS (LIVING OR DEAD)
				YR.	MO.	MO.	YR.	MO.	YR.	
51	F	W	50	20		7	51	6	53	L
52	M	W	35	4	1	7	51	2	54	L
53	F	N	47		2	8	51	10	51	D
54	F	W	37	2	1	8	51	3	53	L
55	F	W	49		9	8	51	10	53	L
56	F	N	24	1	7	10	51	12	51	D
57	F	W	31	4	9	10	51	1	54	L
58	F	W	44	16		10	51	7	53	L
59	F	W	44	3	5	11	51	8	53	L
60	F	W	13	1	6	12	51	4	52	L
61	F	N	34	4	5	3	52	12	53	L
62	F	W	39	12		3	52	12	53	L
63	F	W	47	17		4	52	2	54	L
64	F	N	45	1	11	5	52	4	53	D
65	F	W	24	4	11	5	52	9	52	L
66	F	N	48	16		6	52	2	54	L
67	M	W	44		8	6	52	2	53	L
68	F	W	21	3		6	52	10	53	L
69	F	W	27	5		6	52	10	53	L
70	F	W	34	2		6	52	4	53	L
71	F	W	39	16		6	52	1	54	L
72	F	N	30		4	8	52	8	53	D
73	F	W	27		7	8	52	7	53	L
74	F	W	40	18		9	52	12	53	L
75	F	W	13	1	2	10	52	7	53	L
76	F	W	23	1		10	52	7	53	L
77	F	W	43	2	3	10	52	1	54	L
78	F	W	47	2	8	10	52	1	54	L
79	F	N	15		1	11	52	2	54	L
80	F	W	24	3	2	12	52	2	54	L
81	F	W	30	1	11	1	53	12	53	D
82	F	N	46	1		4	53	10	53	L
83	F	N	51		8	4	53	1	54	L
84	F	W	18		1	4	53	1	54	L
85	F	W	25		5	4	53	11	53	L
86	F	W	34		5	4	53	6	53	L
87	F	N	34	1	10	5	53	2	54	L
88	F	W	41	7		5	53	1	54	L
89	F	W	40	10		5	53	1	54	L
90	F	N	42	1	11	6	53	1	54	L
91	F	W	45	1	4	7	53	7	53	L
92	F	N	31	1	6	9	53	2	54	L
93	F	N	37	2	2	9	53	1	54	L
94	F	W	56	4		9	53	1	54	L
95	F	W	12		3	9	53	2	54	L
96	F	W	41	5	3	9	53	1	54	L
97	F	N	28	2	2	10	53	1	54	L
98	F	N	41	10		10	53	2	54	L
99	F	W	44	15		12	53	2	54	D

TABLE B FOLLOW-UP DATA AND CALCULATION OF SURVIVORSHIP FOR NINETY-NINE PATIENTS WITH SLE

YEARS AFTER DIAGNOSIS (x)	NUMBER OBSERVED X OR MORE YEARS AFTER DIAGNOSIS (O_x)	NUMBER LAST OBSERVED AND ALIVE IN INTERVAL BETWEEN THIS X AND NEXT STATED X YEARS ($_nw_x$)	NUMBER DYING IN INTERVAL BETWEEN THIS X AND NEXT STATED X YEARS ($_nd_x$)	ESTIMATED PROPORTION OF PERSONS SURVIVING TO THIS X WHO:		PERCENTAGE OF PERSONS DIAGNOSED WHO SURVIVE X YEARS (P_x)
				DIE BEFORE NEXT STATED X YEARS ($_nq_x$)	SURVIVE TO NEXT STATED X YEARS ($_np_x$)	
(1)	(2)	(3)	(4)	(5)	(6)	(7)
0	99	3	13	0.133	0.867	100.0
0.25	83	9	2	0.025	0.975	86.7
0.50	72	6	2	0.029	0.971	84.5
0.75	64	8	3	0.050	0.950	82.0
1.00	53	18	6	0.136	0.864	77.9
2.00	29	9	2	0.082	0.918	67.3
3.00	18	12	2	0.167	0.833	61.8
4.00	4					51.5

The calculation of survivorship from these basic data requires first an estimate of the probability that survivors at one anniversary will die before the next. The rationale of this calculation will first be described.

If there were no live withdrawals from observation partway through the interval, the probability that persons starting a given interval would die before the end of the interval would be a simple matter of dividing the observed deaths in the interval by the number starting the interval alive.

If we let $_nq_x$ = the proportion of people alive at anniversary x who die before the next anniversary, $x + n$, then *if there were no living persons withdrawn from observation in the interval*, so that the status of everyone at the end of the interval were known, we would have

$$_nq_x = \frac{_nd_x}{O_x}, \tag{1}$$

that is, the deaths divided by the starters.

However, if some of the starters neither die within the interval nor are known to complete it alive, the observed deaths will be incomplete for the number starting the period.

Different methods of life table construction result from different approaches to estimating these missing deaths but the end results of these various methods are in essential agreement. A simple and widely used formula for deriving the probability of dying in this situation is

$$_nq_x = \frac{_nd_x}{O_x - \frac{1}{2}\,{}_nw_x}. \tag{2}$$

In this form, it appears that a correction has been made on the starting number, reducing it by one-half the living withdrawals to secure an appropriate denominator for the observed deaths. However, this formula may be rewritten so that the correction for the missing deaths among the starters is apparent, that is, a correction for the deaths occurring before the end of the interval among those withdrawn from observation.

If we assume that the withdrawals are followed on the average halfway through the period and that during the remaining half of the period they are subject to one-half the risk of dying

involved in the whole period, then we would expect that among the withdrawals the deaths occurring before the end of the period would be $\frac{1}{2}\ {}_nq_x\ ({}_nw_x)$. We would then estimate that the proportion of the starters who would die before the end of the interval would be

$${}_nq_x = \frac{{}_nd_x + \frac{1}{2}{}_nq_x\ ({}_nw_x)}{O_x}. \tag{2a}$$

Formulas (2) and (2a) are identical except in arrangement. The first form is more convenient for calculation, but the second may have more appeal in indicating that not all the deaths among the persons starting the interval are observed and some must be estimated.

Circumstances under which this formula will be satisfactory are that *within* the intervals chosen for analysis, the death rate does not greatly change, so that the risk of dying in the last half of the interval is approximately one-half that of the total interval, and also that the withdrawals are so spaced through the interval that on the average they occur at the halfway point. It was to satisfy the first of these conditions that the first year after diagnosis was broken into quarters, for the rapid death rate in the first quarter is not characteristic of the rest of the year.

Column 5.—${}_nq_x$ gives the probability that a person alive at x will die before $x + n$, estimated by the application of formula (2) to the data, e.g.,

$${}_{0.25}q_0 = \frac{13}{99 - \frac{1}{2}(3)} = 0.133.$$

Stated in percentage form, 13.3 per cent of the patients diagnosed will be dead 3 months later. Of those who survive 3 months, 2.5 per cent will be dead after another 3 months, and so on.

Column 6.—${}_np_x$ is the probability that a person alive at time x will continue to survive to $x + n$. These figures are simply the difference between unity and ${}_nq_x$, that is, if 13.3 per cent die within the first quarter, 86.7 per cent survive.

Column 7.—P_x gives the percentage of the original number diagnosed who are estimated to survive x years. This is an accumulation (but not by addition) of the probabilities of surviving through the separate intervals. Starting with 100 (if a percentage statement is desired), a "depreciation" curve is obtained by the successive application of the survivorship probabilities given in column 6. That is, of 100 diagnosed, 86.7 per cent survive one quarter year; of these survivors 97.5 per cent survive another quarter, giving 84.5 per cent of the original patients who survive one-half year; of these, 97.1 per cent survive another quarter, giving 82.0 per cent of the original patients surviving 9 months, and so on. By continual multiplication of the survivorship probability by the preceding result, we obtain finally that 51.5 per cent survive 4 years.

This is the survivorship curve plotted in Fig. 4, which was the stated aim of the calculation.

Standard Error of P_x.—

If we let $O_x' = O_x - \frac{1}{2}\ {}_nw_x$. Greenwood's formula for the standard error of P_x may be written:

$$SE_{P_x} = P_x \sqrt{\text{Sum of } \frac{{}_nd_x}{(O_x')\ (O_x' - {}_nd_x)}}$$

where the summation extends from $x = 0$ to $x - n$; that is, the summation starts with the first row of the table and ends with the row prior to that containing the P_x whose standard error is being estimated.

For P_4 we have,

$$\text{Sum of } \frac{{}_nd_x}{(O_x')\ (O_x' - {}_nd_x)} = \frac{13}{(97.5)\ (84.5)} + \frac{2}{(78.5)\ (76.5)} +$$

$$\frac{2}{(69.0)\ (67.0)} + \frac{3}{(60.0)\ (57.0)} + \frac{6}{(44.0)\ (38.0)} +$$

$$\frac{2}{(24.5)\ (22.5)} + \frac{2}{(12.0)\ (10.0)} = 0.027105$$

Then,

$$SE_{P_x} = 51.5\ \sqrt{0.027105} = 51.5(0.165) = 8.5\%$$

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HYPERTENSIVE VASCULAR DISEASE; DESCRIPTION AND NATURAL HISTORY

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TO DETERMINE whether significant modification in the course of hypertensive vascular disease is to be achieved by any specific means (chemotherapy, dietary restriction, surgical intervention), it is essential that its natural history be evaluated clearly. Such an appraisal requires the employment of valid diagnostic criteria and of definitions and terminology permitting accurate, uniform, and acceptable classification. The fact remains (even in discussions conducted by qualified clinical and laboratory investigators) that many of the accumulated data in this field are difficult to interpret because of the paucity of exact statements necessary to provide a sound basis for scientific inquiry.[1]

Therefore, statistical information is presented concerning the histories of 500 patients with hypertensive vascular disease (in part an extension of a previously reported series[2]), none of whom was treated with other than symptomatic measures (reassurance, sedation, and, if complications appeared, bed rest and digitalis). This group is composed of 150 persons followed from before the onset of hypertension until death, and of 350 patients followed from an uncomplicated hypertensive phase until death.

CRITERIA AND DEFINITIONS

Conclusions drawn from this survey or from the clinical experience of others will be of limited value unless there is differentiation between the presence or absence of disease, elimination of artifical and arbitrary groupings into gradations of disease, and clarification of the terminology employed. Before presentation of data, therefore, it is necessary to formulate the criteria used in this clinic and in the present study by which the diagnosis of hypertensive vascular disease and its varying stages is made.

As yet the diagnosis of hypertensive vascular disease cannot be established on the basis of any single criterion. Until some other more precise test is developed, attention must continue to be focused on abnormal diastolic blood pressure values. But "foremost among (the) difficulties is the question of what

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levels . . . are to be regarded as normal and what as abnormal."[3] The overlap in readings under certain physiologic conditions as compared to those encountered in disease makes this distinction impossible. Neither does the statistical procedure of Master and his associates[4] serve to differentiate the healthy from those who are ill, nor do techniques which employ "basal" or "resting" values provide a practical answer as yet.

Therefore, consideration in this study was given first to those factors which are known to give rise to real or apparent elevations of blood pressure but which are not associated invariably with hypertensive disease states. Environmental and psychogenic stimuli provoke major vasoconstrictive reactions in some hyperreactive individuals; acute anxiety attacks may lead temporarily to extreme heights of both systolic and diastolic pressures. Furthermore, the obese arm may produce falsely high sphygmomanometric readings which may be 10 to 15 mm. of mercury above the true intra-arterial tension. Hence individuals with transient rises in blood pressure or minimal elevations related to obesity were excluded.

It was then found necessary to consider the role of arteriosclerosis, as it is known that sclerosis of the aorta and its large branches, through modification of vascular distensibility, can be associated with high systolic blood pressures. However, there is increasing evidence that diastolic values as high as 100 mm. of mercury may be encountered as a result of these and other degenerative changes.[5] For this reason, patients above 50 years of age were not included unless diastolic pressures were in excess of 100, nor were those with diabetes mellitus or known hypercholesteremic states at any age.

Hypertension is suspected in this clinic whenever the diastolic pressure has been recorded as 90 or higher on any occasion, and is defined as *the repeated finding of a casual, diastolic pressure of 90 mm. of mercury or more after the exclusion of those with transient rises in blood pressure, those with marked obesity (unless repeated values are in excess of 105), and those with possible arteriosclerotic causes (unless repeated values are in excess of 100).* There is considerable evidence to support the view that diastolic blood pressures of 90 mm. of mercury should be regarded with suspicion. The very fact that only 6 to 14 per cent of six series involving a total of more than 100,000 persons exhibited single, casual, diastolic values of 90 or above[3] indicates that this is an unusual finding of possible pathologic significance. Second, when multiple blood pressure readings were secured in 2,000 ambulatory, afebrile patients under the age of 50 and selected at random in this clinic, the 136 with repeated diastolic values of 90 or above were all proved subsequently to have unequivocal hypertensive vascular or renal disease. Third, certain symptoms and signs associated generally with hypertensive vascular disease, although conceivably psychoneurotic in origin, coincided with the first discovery of diastolic blood pressure levels of 90 or above even without the patient's knowledge of an elevated pressure; these included nervousness, emotional disturbances, palpitation, vasomotor instability, headache, and elevated metabolic rates without true hyperthyroidism. Finally, and more convincing, such organic complications as cardiac hypertrophy, even myocardial damage and retinopathy, developed in many in the present series

in whom the repeatedly recorded diastolic pressure remained in the 90-100 range over a period of years. It must be recalled always that the absence of hypertension does not exclude previous hypertension; rest, fever, myocardial infarction, cerebral vascular accidents, and drugs may induce the temporary disappearance of an elevated blood pressure even at a late stage in the evolution of hypertensive disease.

Hypertensive vascular disease (primary or essential hypertension) is defined in this clinic as a disorder characterized by *the presence of hypertension (as defined previously) when it is not secondary to a known primary pathologic process* (Table I).

TABLE I. CONDITIONS IN WHICH SECONDARY HYPERTENSION MAY BE ENCOUNTERED

A. Central Nervous System
   1. Increased intracranial pressure (inflammatory, neoplastic, etc.)
   2. Diseases of spinal cord (poliomyelitis, tabes, etc.)
   3. Familial autonomic dysfunction[6]
B. Adrenal and Chromaffin Tissue
   1. Pheochromocytoma
   2. Cushing's syndrome
C. Renal
   1. Vascular and parenchymal damage (embolic, thrombotic, obstruction by tumor or aneurysm, collagen disease, thrombotic thrombocytopenic purpura, acute and chronic glomerulonephritis, pyelonephritis, acute renal ischemia, polycystic disease, amyloidosis, hyperparathyroidism, vitamin D intoxication, urinary tract obstruction, etc.)
D. Toxemia of Pregnancy
E. Coarctation of Aorta
F. Acute Intermittent Porphyria

In this survey, *complications* of hypertensive vascular disease are listed under the pathologic heading of either cardiac hypertrophy, arteriosclerosis, or arteriolosclerosis. The term "*encephalopathy*" is reserved to describe only those patients whose acute cerebral manifestations, characterized by headache, vomiting, convulsions, and even coma associated with a rapid rise in blood pressure, are not accompanied or followed by sensory or motor signs, these being more indicative of thrombotic or other vascular insults.[7]

"Malignant" hypertension is a term which is diffuse in its meaning, prognostic in its implications, and truly a confession of ignorance. It is often contrasted with "benign," another unfortunate and misleading adjective. It is preferred in this clinic to speak of the "*accelerated phase*," a clinical phase characterized by an accelerated velocity, progressive emphasis on and damage to the renal area, and death in uremia unless the course is terminated along the way by coexistent brain or heart damage. Most of these patients show extensive retinopathy, usually with papilledema, but on occasion eye-ground changes are absent or minimal, or if present may even regress. Pathologic examination reveals that the majority have developed a necrotizing arteriolitis involving particularly the vessels of the kidney, retina, pancreas, liver, and periadrenal areas. A few patients, clinically indistinguishable from this group, will show

only extensive arteriolar alterations in the kidneys. It is important, if those with necrotizing arteriolitis represent some superimposed pathogenetic factor at work, to retain them in a separate category; hence the term "accelerated phase" is employed in this survey as a clinical description, and the expression "accelerated phase with necrotizing arteriolitis" is reserved for those in whom there is pathologic confirmation.

HYPERTENSIVE VASCULAR DISEASE—SURVEY OF 500 PATIENTS

To be included in the present series, the following criteria were fulfilled: (1) the establishment of the existence of hypertension as previously described, (2) the documentation of hypertensive vascular disease, as defined previously, and (3) periodic observation *without specific therapy (that is, rigid salt restriction, hypotensive drugs, or sympathectomy) other than symptomatic measures.* Patients who met these requirements were selected only on the basis of being normotensive or in the uncomplicated hypertensive phase when first seen and by the fact that they were followed until death from a cause related to their disease. The majority of the patients studied came from an outpatient clinic population and were urban dwellers. With infrequent exceptions, clinical and laboratory observations were undertaken at least once a year.

Patients were considered to be normotensive when at least three blood pressure determinations of less than 140/90 were obtained on separate occasions in the sitting or standing position in ambulatory individuals, and not recorded during or immediately after acute or febrile illness. The label of hypertension was applied, even in those who later exhibited occasional diastolic values of less than 90, provided that at least three separate hypertensive readings had been obtained and that the subsequent course indicated the development of definite disease. In those cases in which the first appearance of the disorder was preceded by a known period of documented normotension, the time gap between the normal findings and the discovery of hypertension never exceeded two years. Patients were considered to be in the uncomplicated hypertensive phase when their hypertensive vascular disease was not associated with clinical evidence of retinal, renal, cardiac, or cerebral involvement.

The major statistical facts concerning complications and survival of the 150 patients followed from before onset and the 350 additional patients followed from the uncomplicated hypertensive phase are presented in Table II. Although all patients were followed until death, data as to survival time are provided only in the 150 followed before and after onset, since obviously the duration of hypertension in those first diagnosed in this clinic as "uncomplicated hypertensive phase" was usually unknown. Further elaboration of certain features of hypertensive vascular disease and its evolution, as exemplified by this series, is considered under separate headings.

Sex and Race.—It is generally agreed that hypertensive vascular disease is more common in women than men and a 2 to 1 ratio was apparent in this study. About one-third were Negro, a fraction not too different from the population of this clinic at the present time, but larger than that at the time the survey was

started. At first glance, men appeared to run a slightly shorter course than women; the average age at death of Negro patients seemed definitely earlier than that of the group as a whole. However, when it is recalled that men are more prone to the arteriosclerotic process and that socioeconomic factors may

TABLE II. STATISTICAL DATA CONCERNING 500 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

	NO. OF CASES	PER CENT	MEAN AGE		SURVIVAL AFTER ONSET (YR.)	
			AT ONSET	AT DEATH	MEAN	MAXIMUM
Followed from before onset until death	150		32	52	20	
Women	104	69	33	53	20	44
Men	46	31	31	50	19	41
Negro	48	32	32	48	16	40
Followed from uncomplicated phase until death	350					
Total followed until death	500*					
Women	331	66				
Men	169	34				

COMPLICATIONS IN TOTAL SERIES OF 500 PATIENTS	NO. OF CASES†	PER CENT‡	SURVIVAL AFTER SPECIFIED COMPLICATION (YR.)	
			MEAN	MAXIMUM
Cardiac hypertrophy by x-ray examination	335(452)	74	8	18
by electrocardiogram	196(332)	59	6	14
Arteriosclerosis				
Coronary				
Congestive failure	251	50	4	13
Electrocardiogram damage	222	67	5	18
Angina pectoris	82	16	5	11
Myocardial infarction	38	8	4§	15
Cerebral				
Encephalopathy	10	2	1	3
Cerebral vascular accidents	58	12	4§	19
Arteriolosclerosis				
Retinal				
Sclerosis (moderate or advanced)	139(440)	32	6	19
Hemorrhages and/or exudates	62(440)	14	4	21
Papilledema	31(440)	7	1	2
Renal				
Proteinuria (excluding terminal)	212	42	5	19
N retention (including terminal)	92	18	1	10
Accelerated phase (clinical)	35	7	1	2

*Age at death, 52± 9.6 years.

†Figures in parentheses indicate number of cases in which the appropriate observation or test was carried out in order to disclose the complication if present.

‡Per cent of those studied sufficiently to disclose the complication if present; complications which might have occurred during unobserved terminal illness are obviously not included.

§Excluding cases in which the event caused immediate death.

play a part in medical care and supervision, no clear significance can be attached to these variations.

Body Type and Personality.—The pattern of mild or moderate obesity in short and stocky body types appeared fairly frequently in this series, as did various anxieties and neurotic tendencies. Nevertheless, no characteristic habitus or personality framework was discernible although no statistical or analytic study was made to establish this point. Examination of those who survived more than twenty-five years revealed that 80 per cent were women; that obesity was more common; and that extreme variations in arterial tension (very high casual levels falling rapidly to nearly normal values after prolonged rest or sedation), anxiety patterns, and unstable vasomotor reactions were encountered more frequently than in the total group.

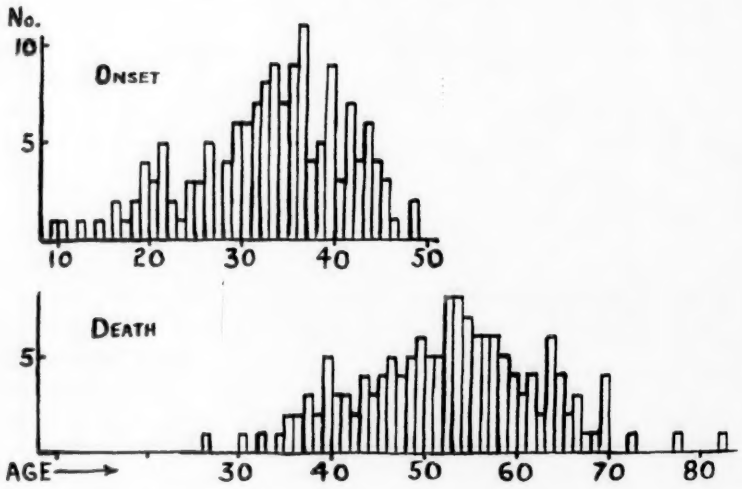

Fig. 1.—Age at onset and age at death of the same 150 patients with hypertensive vascular disease.

Age at Onset.—Hypertensive vascular disease began in this series as early as 9 years of age, but never after the age of 48 on the basis used for its diagnosis in this study (Fig. 1). In the experience of this clinic to date, whenever the documented onset of hypertension occurred after the age of 50, a secondary cause for an elevated blood pressure has been discovered.

Relation of Onset to Pregnancy.—In only fourteen patients was there any evident relationship between pregnancy and the onset of disease. The possibility that hypertension preceded conception could not be excluded in ten instances. These data suggest but a coincidental association and that sustained elevations of blood pressure after a pregnancy are indicative generally of antecedent disease.

Onset of Hypertension; "Tension".—As a rule, in the group followed from before onset, hypertensive vascular disease developed insidiously without the patient being aware of any change until informed of an elevated blood pressure

or until the subsequent appearance of symptoms such as headache. At times, however, the onset was abrupt with a point of transition measurable almost to a day. In twelve instances, the sudden development of a pattern which might be termed "*tension*" has been associated with the initial appearance of hypertension. Without demonstrable psychic trauma, these individuals became tense, restless, hyperkinetic, and emotionally labile. Nervousness, insomnia, and palpitation were common complaints. These characteristics were conspicuous by their absence in the previous background of these patients and were recognized at times by the subject, his relatives, or his physician as a prominent new development. Others in the present series have acquired this pattern insidiously and later in their course. Once present, it has fluctuated in its intensity but has not disappeared entirely except in relation to specific therapy.

Investigation has shown that these patients with "tension" are likely to have rapid heart rates and elevated metabolic rates without true hyperthyroidism. The presence of pheochromocytoma has been excluded by pharmacologic tests. The picture of "tension," although similar indeed to that of common psychoneuroses, is modified dramatically in most instances by thoracolumbar sympathectomy and by the alkaloids of *Rauwolfia serpentina*. It must be regarded as a feature characteristic of some patients with hypertensive vascular disease, as it is present in a substantial number of cases.

Duration of Life.—When followed from onset until death, the average patient with hypertensive vascular disease in this series lived for a period close to two decades. The most rapid course was that of a patient who developed the accelerated phase de novo and was dead (with autopsy evidence of advanced necrotizing arteriolitis) in fourteen months. Long survival was not a rarity; three of the present series lived for periods longer than forty years. Comments have been made that, for unknown reasons, great variety exists in the mortality rate as reported in different series.[8] It is suggested that the duration of observation is the more important variable rather than the mortality rate, for the average age at death in the present series (52 years) is comparable to that of most of the clinical and pathologic surveys in the literature.

Uncomplicated Hypertensive Phase.—The average patient in this study spent about three-quarters of his hypertensive life in an uncomplicated phase. Approximately one-third of the patients were without symptoms throughout this period, and in three-fourths of those with symptoms (that is, fatigue, nervousness, dizziness, palpitation, insomnia, headaches, and so forth), the complaints were inconstant or disappeared without specific measures. Lability of blood pressure measurements was evident in about three-fourths of the group. Excluding terminal cases, the mean duration of life after the first recording of a systolic blood pressure greater than 200 or a diastolic greater than 120 was just under nine years. In the group studied, neither the initial level nor the maintained height of the *casual* blood pressure of those first observed in the uncomplicated phase showed any correlation with symptoms, rate of progression, or subsequent development of complications. This was not true, however, of patients with fixed high diastolic levels which remained elevated following rest

or sedation; such patients varied greatly in their symptomatology, but with individual exceptions tended to develop complications more quickly.[2]

Complications of Hypertensive Vascular Disease.—In Table II are listed complications, their frequency, the mean duration of life after their development, and, to illustrate the extreme variety of this disorder and the dangers in making individual rather than statistical prognostications, the maximum period of survival observed in any single individual after a complication had appeared. However, in the total series of 500 patients with hypertensive vascular disease, multiple complications were the rule. The average survival figures refer both to uncomplicated cases and to those with complications; patients with more than one complication are listed, therefore, in more than one category. One can only conclude, were all subjects to have acquired but a single complication, that some might have lived longer than is indicated. Similarly, the data concerning duration of life relate to the time a complication was recognized; the cardiac hypertrophy or damage, retinal change, and so forth, might well have antedated their discovery.

At least temporary reversibility of retinal hemorrhages and exudates was noted in about one-quarter of those with this complication; papilledema regressed definitely in only two instances; otherwise no convincing evidence of "improvement" in signs of organic involvement was discernible. The heart size diminished occasionally, but only in association with relief of concomitant congestive failure; the electrocardiogram "improved" only in the course of the evolution of a myocardial infarction; the degree of proteinuria was reduced to a significant extent only in those patients with congestive failure.

The data obtained in this series would indicate that cardiac hypertrophy was the complication of least prognostic import, although contributory perhaps to the lowering of cardiac reserve in the presence of coronary arteriosclerosis. Control studies in normotensives aged 45-55 in this clinic reveal such a high incidence of mild to moderate retinal sclerosis (irregularities of the arterial lumen, thickening at arteriovenous junctures, and the like) as to make this sign of doubtful significance. Most of the remaining complications, occurring singly or in combination, were all compatible with a mean survival period of about four or five years. Nitrogen retention and papilledema, however, stood out conspicuously as the signs of greatest danger, being the findings so often associated with terminal disease or the accelerated phase.

It is noteworthy that encephalopathy, as defined previously, was a rare event encountered in this series only in patients with very advanced disease. The accelerated phase (clinical) developed in thirty-five patients (7 per cent), in thirty-three instances after a period of known hypertension, twice as the first indication of disease; thirty-one of the thirty-five were men; and fifteen of the eighteen autopsied patients had widespread necrotizing arteriolitis, the remainder showing only nephrosclerosis.

Causes of Death.—Just as multiple complications were more frequent than single, so multiple rather than single factors led to death in most cases. Division into primary (or predominant) and contributory factors must therefore

be made. In the present series the cause could not be determined in 43 per cent, mostly instances of sudden death occurring at home or elsewhere. Congestive failure was the primary event leading to the death of 22 per cent of the series, but was a contributing factor in 38 per cent. Cerebral vascular accidents accounted for 9 per cent, myocardial infarction and the complications of renal insufficiency for 6 per cent, and 2 per cent died with rupture of arteriosclerotic aneurysms. Uremia was a contributory part of the picture prior to the death of 10 per cent. In 12 per cent of the series, multiple factors seemed of such equal importance that no single cause could be favored.

SUMMARY AND DISCUSSION

The major objective of the present report has been to describe hypertensive vascular disease and the course of a group of patients with this condition, more from the standpoint of providing a basis for inquiry rather than of portraying a full or final characterization. The large variations in reported incidence, in rates of progression, in mortality rates, and in response to therapy provide a strong argument that a real need exists for uniform definitions and common methods of description and classification. It is clear, at the present time, that this is not an easy task. No sharp line separates normal from abnormal blood pressure levels; the recognition of hypertension as defined usually presents no problem but at times may require months and years of careful observation before its documentation; and the diagnosis of hypertensive vascular disease is made in patients in whom hypertension is established and in whom no basis for secondary hypertension is discernible.

No survey of the evolution of a disease, observed in one geographical area and defined by manifestations rather than by more definitive characteristics, can be freed entirely from the stigmas of selection. One can only argue that the patients reported in this survey were chosen on the basis of certain diagnostic criteria rather than on the character or duration of their subsequent course. Hypertensive vascular disease emerges more and more as a chronic illness, more common in women, beginning as a rule in early adult life, related little if at all to pregnancy, and persisting for an average period of two decades before its secondary complicating pathologic features cause death at an average age fifteen to twenty years less than the normal life expectancy. Hypertensive vascular disease may progress at a highly variable rate, but on the whole the patient with this disorder spends more of his hypertensive life with insignificant symptoms and without complications. His eventual troubles are related less to his blood pressure than to his cardiac hypertrophy, arterio-, and arteriolosclerosis, with death from cardiac complications heading the list of ultimate eventualities. Encephalopathy and the accelerated phase with necrotizing arteriolitis are uncommon occurrences in the natural history of the disease. The proper evaluation of therapy must rest on comparison with the disease as it truly exists, not on comparisons based on artificial yardsticks maintained for inadequate periods.

CONCLUSIONS

1. An appraisal of the natural history of hypertensive vascular disease has been made following a description of the diagnostic criteria, definitions, and terminology employed.

2. Hypertension is defined in this study as the repeated finding of a casual diastolic pressure of 90 mm. of mercury or more, after the exclusion of patients with transient rises in blood pressure, and with higher limits set for those with marked obesity or with disorders possibly productive of arteriosclerosis of the aorta and its large branches; hypertensive vascular disease is a diagnosis of exclusion.

3. Complications of hypertensive vascular disease are described in terms of their underlying pathology rather than in the form of arbitrary groupings into gradations of disease; the term "malignant hypertension" has been discarded.

4. Based on the diagnostic criteria employed in this study, a survey has been made of the evolution of 500 patients with hypertensive vascular disease, followed without specific therapy from before the onset of hypertension (150) or from an uncomplicated hypertensive phase (350) until death from a cause presumably related to their disease.

5. The average patient in this study survived close to twenty years, having spent three-quarters of his hypertensive life in an uncomplicated phase.

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THE RESULTS OF MEDICAL TREATMENT OF PEPTIC ULCER

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A LONG-TERM study of the results of medical management of peptic ulcer was initiated in the Follow-up Clinic of the Presbyterian Hospital about twenty years ago. A series of patients with gastric or duodenal ulcer were placed on conservative treatment. These persons were seen periodically, at intervals of six months, or oftener if necessary, in order to record the variations in the natural history of the disease. It was hoped that the accumulated data would serve as a basis for comparison with the results of surgical treatment and for reference in the evaluation of newly proposed remedies for peptic ulcer. The results of this study constitute the chief source of material for the present report.[1-5] An analysis of those factors which appear to influence prognosis will be presented.

Most of the patients who were included in the follow-up study were initially hospitalized for a period of intensive treatment. Medical therapy consisted chiefly of frequent bland feedings, moderate amounts of alkalies between feedings, mild sedation, and, at times, antispasmodics during active symptoms, and for a period of time thereafter. Reassurance and assistance in environmental readjustment were attempted when feasible. After discharge from the hospital, the patients followed a restricted diet and took medication for variable intervals of time. The majority of them gradually resumed a normal or self-modified diet.

The results of medical treatment may be divided into immediate and long-term.

IMMEDIATE RESULTS

The majority of patients with uncomplicated ulcer experience prompt and complete symptomatic relief after institution of medical treatment. Pain usually disappears completely within the first week and frequently within a day. In a group of 233 individuals with duodenal ulcer admitted to the Presbyterian Hospital for medical therapy, the pain disappeared entirely within two weeks in 74 per cent of patients. Occult blood, when present in the stools, rarely persisted for more than ten to fourteen days.

The rate of healing of the ulcer crater, as shown on serial x-ray study, is extremely variable. The healing time of gastric ulcer averaged approximately

six to eight weeks in those patients in our series in whom radiologic study was carried out with sufficient frequency to establish the time interval with accuracy. Some lesions disappeared in less than two weeks, and in a few patients who at first declined surgical therapy x-ray evidence of a crater in the stomach persisted for many months before gastric resection was carried out. Gastroscopic studies[6] of the rate of healing of ulcer in the stomach have also shown an average healing time of about six weeks. The rate of healing is not always related to the size of the ulcer crater, and some large lesions may disappear rapidly while small ones may decrease in size relatively slowly.

The healing time of duodenal ulcer has also been reported to average approximately six weeks. In duodenal ulcer, the rate of healing is often impossible to determine accurately because of technical limitations and the difficulty in distinguishing between a crater shadow and barium trapped between mucosal folds in a deformed duodenal bulb. In a small group of individuals with duodenal ulcer studied in this clinic, it was found that the crater in the duodenum disappeared within two months in three-quarters of the patients.

After preliminary intensive treatment with the relief of pain, many patients with ulcer still continue to suffer from mild upper digestive complaints such as fullness and belching, as well as occasional very transitory episodes of pain. As a rule, x-ray study of such patients who continue to have minor complaints fails to reveal evidence of an active ulcer. It is believed that symptoms of this type are due to some poorly understood persistent motor dysfunction.

Factors Which Modify Immediate Results of Treatment.—A variety of factors appear to influence the immediate result of medical treatment in uncomplicated ulcer. In ambulatory patients the probable commonest cause for an unsatisfactory result is failure to follow the prescribed regimen. Heuer[7] calculated that about 60 per cent of ambulatory patients successfully follow a regimen with reasonable care.

There is general agreement that emotional factors may play an important role in response to treatment, although such factors are difficult to appraise. It is commonly observed that hospitalization, without other change in therapy, is often followed by prompt and dramatic symptomatic relief in patients who have hitherto been responding poorly to treatment. Wartime experience with soldiers with peptic ulcer seemed to emphasize the effect of the emotional status on the symptomatic response to treatment.[8-10] A number of observers noted that the results of conservative therapy were often less satisfactory than those encountered in civilian life. There appears to be a correlation between a delayed symptomatic response to treatment and poor morale. Certain observations also suggested that there was an actual delay in healing of duodenal ulcer in some soldiers as contrasted with civilians.

Obviously the presence of complications such as gross hemorrhage, perforation, and obstruction modifies the immediate result in peptic ulcer.

The presence of persistent pain constitutes a problem which merits special consideration.

In a previously reported analysis of 233 patients who were hospitalized for medical treatment of duodenal ulcer,[2] it was found that sixty-two patients continued to suffer from pain for more than two weeks after hospital therapy had been instituted. In most instances, pain was ultimately relieved on continued medical therapy. The mechanism responsible for the persistent pain was not always apparent. Psychiatric problems appeared to play a role only in a minority of patients of this type. Those patients who came to operation at a subsequent date usually had extensive scarring in the region of the duodenum, but this was not a constant finding. Similar anatomic evidence of chronicity is also frequently encountered in many patients with duodenal ulcer without pain of unusual severity.

A recent study by Haubrich, Roth, and Bockus[11] is of interest in this connection. These authors reviewed a series of patients who, at operation for ulcer, had been found to have walled-off perforations. About 65 per cent of these individuals were considered to have suffered from intractable pain. Their studies led the authors to conclude that intractable pain was not a characteristic sign of walled-off perforation. Ineffectiveness of medical therapy in relieving pain is probably due, in large measure, to an extending inflammatory process, whether the ulceration is intramural or perforating.

Other factors such as hypersecretion of gastric juice or associated gastritis have been suggested as possible reasons for intractability to medical therapy. Evidence in support of these possibilities seems to be scanty. Haubrich, for example, found no evidence that excessive hyperchlorhydria was correlated with further penetration of an established ulcer.

LONG-RANGE RESULTS OF MEDICAL TREATMENT

After satisfactory relief of symptoms and disappearance of the ulcer crater, as seen on radiologic examination, the subsequent clinical course of patients with peptic ulcer is extremely variable. The majority of individuals experience a recurrence at some time in the future. In our clinic, 78 per cent of patients with duodenal ulcer experienced one or more recurrences during the subsequent five years of medical management. Of 101 patients treated medically for gastric ulcer, all but two individuals ultimately had a recurrence. In many reported follow-up studies, the incidence of recurrence varies from 46 to 93 per cent within a five-year period after initial observation and treatment.[4] Most patients can again be relieved by a resumption of strict medical treatment.

A continuous type of survey of patients with ulcer over a period of years fails to reveal a consistent pattern of behavior of the disease in most individuals. Recurrences seem, for the most part, unpredictable. When recurrence does occur, it may be attributed by the patient to emotional stress, to dietary indiscretions, to a variety of miscellaneous stress factors such as upper respiratory or gastrointestinal infection, or to incidental operation. In an appreciable proportion of individuals, there is no apparent precipitating factor.

In our series of patients with duodenal ulcer under conservative management, the average recurrence rate was once every 2.1 years after an initial period

of intensive hospital therapy. In gastric ulcer, the recurrence rate was once every 2.4 years. There appears to be very little difference in the recurrence expectancy whether the ulcer is gastric or duodenal.

The prescribed dietary regimen, after initial hospital therapy, was a bland type of diet with six feedings. The food was puréed for the first one to two months, after which time grinding of the food was discontinued. Medications were usually discontinued about one month after discharge from the hospital except for the use of alkalies as needed for epigastric distress. The majority of the patients did not adhere to dietary instructions for more than a few months and discontinued in-between-meal feedings or adopted more liberal diets. A number of patients did adhere strictly to the dietary regimen for one year or more.

Comparison of the symptomatic course during the first follow-up year of those patients with duodenal ulcer who followed a rigid diet with those who interrupted or discontinued these diets was of interest. A recurrence of symptoms was noted as frequently in patients who followed the prescribed regimen as in those who did not. No evidence was found that prolonged adherence to a very careful type of diet served to prevent recurrence of symptoms after initial healing of the lesion.

Certain patients have been found, as a group, to have a better than average follow-up course. Thus, a group of patients with duodenal ulcer who never required hospitalization were found to have recurrences on an average of once every four years. Few individuals in this series had ever experienced any complications, and they therefore constitute a select group. Patients with a short history of symptoms prior to initial definitive treatment also are reported[4] to have an outlook which is somewhat better than average.

An initial slow symptomatic response to hospital treatment is, in our experience, a bad prognostic sign. In the study previously cited[2] of patients with protracted pain, it was found that individuals with duodenal ulcer who continued to experience pain for more than two weeks on ideal hospital management subsequently continued to fare badly as a group. They were found, during follow-up observation, to have recurrences once every 1.2 years, a rate almost twice as frequent as the average. A number of these individuals ultimately required surgical intervention. As indicated earlier, the reason for resistance to therapy was not always to be found in the anatomic changes encountered at operation. It should be added that a poor follow-up course was not uniformly encountered after an initial slow response to therapy, and many individuals of this type had a fairly satisfactory subsequent clinical course under conservative management.

GROSS HEMORRHAGE

It is generally recognized that patients with a history of repeated hemorrhage from ulcer have a poor prognosis. In an earlier study of a group of patients with a history of two or more preceding gross hemorrhages due to duodenal ulcer, it was of interest that the actual recurrence rate of ulcer symptoms was essentially the same as in our patients who never had bleeding: namely, one

recurrence every two years. This observation is in accord with the view that hemorrhage in ulcer is simply an accident which frequently results from the location of the lesion in an area where a blood vessel becomes involved.

Although there is general agreement that the occurrence of multiple hemorrhage is a bad prognostic omen, it is difficult to obtain precise documentary evidence to prove it. We have, therefore, recently reviewed the records of a larger series of patients with bleeding in an attempt to establish more precisely the risk which is implied by a history of one or more hemorrhages.

The records were reviewed of 327 patients with duodenal ulcer who had a history of hemorrhage at any time. This group represents most of the patients with a history of hemorrhage who were hospitalized during the decade 1928 to 1937 inclusive, an era in which surgical intervention was much less frequent than it is today. If the patients were continued under medical observation after 1937, the subsequent clinical course was included in the survey. An analysis was made of the frequency of recurrent hemorrhage following the first bleeding episode, during the total recorded period of the disease. The majority of patients had been admitted to the hospital at the time of their first bleeding episode. However, a considerable number gave a history of one or more hemorrhages at some time preceding their initial hospital visit. For purposes of this analysis, it was necessary to include the hemorrhages which had occurred prior to observation at this hospital. The clinical course subsequent to an initial hemorrhage was recorded by direct follow-up observation in the Clinic for a total period of 1,172 patient years. The period of time which had elapsed after an initial hemorrhage, which was only documented in the patients' histories before they came to this hospital, was 460 patient years.

The number of patients, the proportion who continued under medical observation, and the duration of observation are shown in the accompanying tables (Tables I and II). Seventy-four patients were lost to conservative observation within the first six months after a single hemorrhage and therefore are not included in the analysis of risk of subsequent hemorrhage. A considerable number of patients were lost to observation under medical care after two or more hemorrhages, but their clinical course until that time is included in this survey. For the group who were followed, the average period of time for which information is available was 6.5 years.

TABLE I. DISTRIBUTION OF HEMORRHAGES IN 327 PATIENTS WITH HEMORRHAGE DUE TO DUODENAL ULCER

NO. OF HEMORRHAGES	NO. OF PATIENTS	CASES FOLLOWED	AVERAGE SUBSEQUENT FOLLOW-UP (YR.)	CASES NOT FOLLOWED CONSERVATIVELY		
				OPERATION	LOST	DIED
1	186	112	5.5	31	35	8
2	68	29	3.1	18	15	6
3	40	14	5.6	13	13	0
More than 3	33	33	4.5	—	—	—

TABLE II. NUMBER OF RECORDED YEARS IN PATIENTS FOLLOWED

	NO. OF PATIENTS	TOTAL RECORDED PATIENT YEARS	AVERAGE FOLLOW-UP (YR.)
Total followed	253	1,632	6.5
After second hemorrhage	102	448	4.3
After third hemorrhage	47	227	4.8

After the initial hemorrhage, 112 of the patients who were followed had no further bleeding during the period of observation (Table III). In contrast, 141 patients who bled more than once were followed. The collective period of recorded history for the entire group was 1,632 patient years, during which time there occurred 273 hemorrhages or an average of one hemorrhage every six years following the initial bleeding episode.

TABLE III. PER ANNUM INCIDENCE OF FURTHER BLEEDING AFTER ONE, TWO, OR THREE HEMORRHAGES IN DUODENAL ULCER

	NO. OF CASES FOLLOWED	NO. WITH RECURRENT BLEEDING	TOTAL RECORDED PATIENT YEARS	TOTAL SUBSEQUENT HEMORRHAGES	HEMORRHAGES PER ANNUM
Total group	253	141	1,632	273	1 in 6 yr.
After second hemorrhage	102	73	448	136	1 in 3.3 yr.
After third hemorrhage	47	33	227	62	1 in 3.7 yr.

Following two hemorrhages, there were 102 patients on whom data were available concerning their subsequent course under conservative management. The incidence of subsequent bleeding was found to be 136 hemorrhages in 448 patient years, or once every 3.3 years.

After three hemorrhages, the subsequent hemorrhage rate proved to be once every 3.7 years.

These data suggest that there is a pronounced increase in the risk of further bleeding in individuals who have experienced more than one hemorrhage from duodenal ulcer. This is in accord with general clinical experience.

It should be pointed out that these statistical data are open to criticism for a number of reasons. A considerable number of the recorded hemorrhages occurred prior to the time that some of the patients first came under observation, and one must depend almost entirely on the histories of the patients for information concerning this period. Further, no data are available concerning the natural history of some patients after a given time, either because they were lost to observation or because they were operated upon.

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PYLORIC OBSTRUCTION

The existence of pyloric obstruction in individuals with duodenal ulcer is not necessarily a bad omen if the obstruction responds to conservative treatment. A group of thirty-six patients with duodenal ulcer were observed who had a transitory six-hour residue of less than 50 per cent of the barium meal present at the onset of treatment. Symptoms disappeared within three or four weeks under conventional therapy. The subsequent clinical course compared satisfactorily with that of other individuals who had not obstructed. Persistent pyloric obstructions not yielding to medical management, which includes adequate nightly lavage, are usually followed by unsatisfactory results if medical treatment is continued.

GASTRIC CARCINOMA

The debatable problem as to whether the presence of a benign gastric ulcer predisposes to the development of gastric malignancy is beyond the scope of the present discussion. Experience in this clinic has lent support to the belief that some such tendency does exist. Among 101 patients with convincing evidence of benign gastric ulcer, followed for an average period of 5.6 years, five patients were observed to develop gastric carcinoma from three to nineteen years later, an incidence which exceeds the expectancy in the general population of comparable age more than tenfold. In contrast, no case of gastric cancer was observed to develop among 233 patients with duodenal ulcer followed for an average period of 6.9 years. There is apparently a somewhat increased tendency for individuals in the gastric ulcer group to develop cancer.

SUMMARY

The results of conservative therapy in gastric and duodenal ulcer, as observed at the Presbyterian Hospital over a period of years, have been summarized. The average healing time of gastric ulcer, and probably also of duodenal ulcer, is approximately six to seven weeks. The basis for symptomatic intractability or delayed healing is often difficult to evaluate, although emotional factors may play a role. In general, the immediate results of medical therapy for uncomplicated gastric or duodenal ulcer are satisfactory.

After healing of the lesion, medical management probably has little influence on the natural course of the disease. The majority of patients ultimately experience recurrences. The recurrence rate in this series of patients has approximated once every two years in both gastric and duodenal ulcer. The long-term outlook is largely unpredictable in a given patient. However, a slow initial symptomatic response to therapy is a bad prognostic sign.

The risk of recurrent hemorrhage following an initial bleeding episode was about once every six years in this series. After a second hemorrhage, the subsequent risk of bleeding was almost doubled. It appears that a tendency to hemorrhage is an anatomic accident attributable to the location of the ulcer.

The development of a gastric carcinoma was observed in five of 101 patients with evidence of benign gastric ulcer who were followed on conservative therapy.

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CARE OF THE LONG-TERM PATIENT

A Summary of the National Conference*

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THE Commission on Chronic Illness is a creation of the American Hospital Association, the American Medical Association, the American Public Health Association, and the American Public Welfare Association.

For some years, each of these organizations has been increasingly aware of the magnitude and importance of the problems of chronic illness. Although each was intimately concerned with one or more aspects of the problem, no one of them could move far toward its solution without encountering the need for help and advice from the others.

In 1945 the four groups took a concerted step in the attack on chronic illness by forming the Joint Committee on Chronic Illness.

By the end of the two-year life of this Joint Committee, it was clear that an independent organization under proper auspices would be a powerful instrument for review and assessment of the chronic illness problem. Accordingly the four sponsors of the Joint Committee planned the establishment of a national commission to study the many aspects of the problem and to develop specific long-range plans.

The Commission came into being in May, 1949, with Mr. Leonard W. Mayo as its chairman. It has thirty-five members representing the medical and other health professions, industry, labor, agriculture, education, welfare, religion, journalism, law, the social sciences, and the general public. Each member serves as an individual rather than as a representative of an organization. Advice and consultation from any member of a panel of thirty-seven technical advisors is available.

The Commission's founders have regarded it as an instrument to bring order, cohesion, and direction to the many related but unintegrated efforts to prevent and control chronic illness and to minimize its disabling effects. Since its founding the Commission's philosophy and actions have been supported financially

*The National Conference on Care of the Long-Term Patient was held in March, 1954, under the auspices of the Commission on Chronic Illness and sponsored by the American Hospital Association, American Medical Association, American Public Health Association, American Public Welfare Association, and the United States Public Health Service.

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and otherwise by two additional national professional associations; seven national voluntary organizations in the health field; the National Health Council and the Public Health Service; three leading foundations; four large life insurance companies; and a university.

At its first meeting the Commission decided that it would attempt to accomplish three main objectives: to gather and transmit information on current activities and plans designed to cope with the many-sided problem of chronic illness; to make or have made such new studies as seem most needed to provide a sound basis for planning in this field; and from this information and these studies, to formulate suggested programs of action by national, state, and local agencies and groups.

The Commission early decided that it would be able to conduct only a limited amount of research and that for implementation of its goals it would rely primarily on aiding and stimulating research by others, and on national conferences called under its auspices.

The first such conference, called in 1951, took as its subject the preventive aspects of chronic illness. Its recommendations have already found wide use in medical schools, schools of public health, and elsewhere in professional education, and to a lesser extent in community planning.

The Conference on Care of the Long-Term Patient, held in Chicago in March, 1954, was the second of the Commission's national conferences. The Public Health Service joined with the Commission's four founders in sponsoring it, and forty national organizations in the health field participated officially.

The objectives of this conference were:

To identify the requirements of the long-term patient in various stages and severity of his illness;

To examine existing methods of providing care, explore new methods, and develop principles which should govern needed changes;

To suggest patterns for desirable relationships between services, facilities, and programs;

To recommend various ways to improve the financing of long-term care;

To establish direction and suggest next steps for local, state, and national programs for the care of the long-term patient.

Early in the planning a pattern was devised which would enable the Commission to draw technical help from experienced people all over the country. About a year ago, the subject matter was divided among five major committees. These committees and their chairmen were:

The Patient at Home: Dr. Martin Cherkasky, Director, Montefiore Hospital, New York;

The Patient in an Institution: Dr. Anthony J. J. Rourke, Executive Director, Hospital Council of Greater New York;

Integration of Facilities and Services: Dr. Milton Terris, Assistant Dean for Postgraduate Education, School of Medicine, University of Buffalo;

Research: Dr. Thomas Parran, Dean, Graduate School of Public Health, University of Pittsburgh;

Financing: Dr. Theodore G. Klumpp, President, Winthrop-Stearns, Inc.

Within the five committees, twenty-eight study groups were set up, and each was assigned a limited segment of the problem with which its parent committee was concerned.

Each study group was centered in a city with successful experience in the subject under study and was built around a nucleus of persons experienced in that particular subject and intimately concerned with it, that is, the operators of programs, services, or institutions. Each group was augmented by other members in a position to have a valuable but different point of view, such as the users of a service or those involved in financing. The plan was that each group would examine the contribution being made, or that could be made, by a particular kind of program or service.

In the ten months preceding the Chicago Conference, these small specialized study groups held an aggregate of over sixty meetings in a dozen different cities. Their reports were extremely useful in identifying the issues most in need of further study and discussion. They also provided a body of factual information for the use of the conference delegates.

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At the Conference the members of the twenty-eight study groups were reshuffled into twenty discussion groups. The representation of disciplines and experience within these discussion groups was broader than had been the case with the study groups, so that the subjects and services under study by the discussion groups could be related to a wide range of other subjects and services. Thus, each discussion group included members of pre-Conference study groups on its subject, members of other study groups, and individuals who as delegates to the Conference were participating for the first time in its work.

One of the early decisions in planning for the 1954 Conference was that it would exclude from consideration the large group of chronically ill whose minor impairments lend themselves to the short-term care ordinarily available in most communities.

Thus, for discussion purposes "long-term patients" included only those suffering from chronic disease or impairments who require a prolonged period of care, that is, whose who are likely to need or who have received care for a continuous period of at least thirty days in a general hospital, or care for a continuous period of more than three months in another institution or home. "Care" is considered to include medical supervision or assistance in achieving a higher level of self-care and independence.

About 5.3 million people meet this definition of long-term patient. The Conference was focused on the health services needed by these 5.3 million people.

An important consideration in formulating the five committees defined previously was the need for a workable approach to a many-faceted problem, which in its entirety is so big as to seem overwhelming. Of course, in providing care to people, the problems of long-term care cannot be compartmentalized into five or any other number of neat packages. But it seemed imperative, for purposes of study, to try to disentangle some of the interlocking pieces.

In trying to report the highlights of the Chicago meeting, I face the same dilemma which confronted us in the pre-Conference phase: how to approach a many-sided subject of gargantuan proportions. There were certain basic

considerations that cut across the special area of concern of all groups. Financing is basic, for example, and one cannot discuss any phase of long-term care without getting into financing. The same is true of integration of facilities and services, for integration or the lack of it affects quality and availability of services and their cost. Research also runs through all the reports, because each committee came upon research needs in its area of primary responsibility.

It is a good and healthy sign that the committees and their discussion groups refused to be confined within narrowly proscribed areas. Refusal to compartmentalize care is a prerequisite to the day when everywhere the patient will be looked upon as a whole person in his particular social and family setting and in a particular stage of his illness, and not as a "case" or the subject of a particular diagnosis and static degree of disability.

In this regard I digress long enough from the committees' specifically assigned subjects to comment on the disposition of the first objective of the Conference. This was to "identify the requirements of the long-term patient in the various stages and severity of his illness." Nearly all the committees and discussion groups dealt with this subject. They reached a heartening unanimity on the general content of their findings. Of great importance in its implications for future action in communities all over the country, and also in its influence on recommendations, was the oft-repeated tenet that the long-term patient needs to be looked upon as an individual, whole person.

One discussion group introduced its report with the statement that "the patient with a long-term illness needs to be identified as a person and not as a disease or a focus of a program." Another group, discussing the long-term patient in the general hospital, emphasized individual people rather than disease categories. A discussion group on outpatient departments said that high quality care must necessarily be concerned with provision of care for the total patient.

Other discussion group reports carry such statements as these:

"Too much rehabilitation is done on the disease—and not enough for the total patient." "It is mandatory to have in any type and size of hospital, personnel who think along the line of 'total patient needs.'" "The patient should be considered at all times as an individual with specific relationship to his family and the community."

This approach to patient care was further emphasized by the representatives of the sponsors when they addressed the banquet session of the Conference. Mr. Maurice Norby speaking for the A.H.A., Dr. George Lull for the A.M.A., Dr. Dean Clark for the A.P.H.A., Miss Loula Dunn for the A.P.W.A., and Dr. Leonard Scheele for the Public Health Service all restated the determination of the organizations they represented to work ever more closely in concert on the problems of long-term care.

Coupled with this emphasis on the whole patient was a frequently expressed appreciation of the nonstatic nature of long-term illness. A committee report said: "A person's chronic illness is characterized not only by its length but also by the changes which occur in his condition and which dictate changes in his care and treatment."

A discussion group put it in these words:

"The long-term patient's overall needs are not static. It is important, therefore that his situation be revaluated periodically." Another group said: "A periodic reevaluation must be done to assure proper recognition of changes in the patient's needs and appropriate modifications of the treatment plan." There must be cooperation among facilities "so that patients may be transferred to and from a community or a facility as needed, as the condition of patients varies, for proper treatment."

In connection with the needs of the chronically ill, committees recognized that medical care is now geared to acute illness. Thinking among the general public and within professional groups is directed to acute illness rather than to illness in general (least of all to chronic illness), and this thinking is reflected in program arrangements and facilities. Attitudes must be thoroughly revised properly to care for prolonged illness, since there are fundamental differences in the needs of patients with acute and chronic illness.

In acute illness, where the onset is sudden and the course of illness usually brief, the patient and the family often have sufficient resources, financial and emotional, to cope with the situation. However, in chronic disease the onset is insidious and by definition the course of illness is long. Families are drained emotionally and economically. Associated with all serious chronic illness are important dislocations in relationships between the patient, his family, and society. In treating acute illness, the doctor can provide virtually all the care, with some assistance in more severe cases from the nurse, because the family is able to cope with the situation. In chronic disease, much more is needed than the skills of doctor and nurse. Social service, occupational therapy, physical therapy, nutrition, rehabilitative services, all of these of relatively little importance in acute illness, are of prime importance in the care of the chronically sick.

The long-term patient needs, in addition to definitive medical care, the kinds of services that will restore his morale, help him adjust to an altered life situation, and motivate him in the uphill struggle toward rehabilitation.

Of paramount importance to the long-term patient are social aspects of care: food, housing, financial problems, family relationships, education, vocational problems, recreational needs, and so forth. These may often require considerably more time and effort than the purely medical aspects, and good integration and coordination of services and facilities is one of the most promising means of assuring that they are not neglected.

The Committee on the Patient at Home had before it the statement that of the 5.3 million long-term patients, four million (almost 80 per cent) are receiving care outside of an institution. Even more should be cared for outside of institutions but cannot be at present because of lack of facilities and services for noninstitutional care. For example, it was pointed out that patients linger in hospital wards because, among other reasons, there are too few home care programs or rehabilitation centers for outpatient service.

The study group on mental hygiene and treatment services estimated that, on the baiss of surveys of all types of patients in psychiatric hospitals, from 10 to 30 per cent of those now cared for in hospitals could live in the community.

A survey in one state, California, which has a comparatively well-developed program for nonhospital mental hygiene and treatment, indicates that about 55 per cent of the patients aged 60 and over admitted to state mental hospitals might more properly have received care in their own communities if adequate facilities existed for home and congregate care, including nursing homes and homes for protective living.

From the point of view of the expense and difficulty of building and staffing additional hospital facilities, the importance of noninstitutional care is quite obvious. Perhaps less obvious but even more important is the desirability, from the sick patient's point of view, of remaining within the shelter and security of his own family, at home.

A series of obstacles stand in the way of the private physician's attempt to care for the long-term patient at home:

1. The services required for adequate care in the home are frequently not available. Without the well-trained visiting nurse, housekeeping service, or visiting physical therapist, the physician may have no alternative but to recommend institutional care. In some cases, a loan service for hospital beds, wheel chairs, and other equipment may be the difference between staying at home or going to a hospital.
2. Even when such services are available, the physician may be unaware of their existence or may neglect to use them because such use has never become incorporated in his habits of professional practice.
3. Individual services for the patient at home may exist in several different agencies but may be so badly coordinated that they cannot be brought to bear effectively on the patient's needs.
4. Lack of financial resources available to pay for physician and other services rendered in the home may force admission of the patient to an institution supported by public funds.

The Committee agreed that the private physician's responsibility with respect to the diversified and complex needs of a long-term patient is to bring to the patient all services required for optimum care. To fulfill this role he must have the assistance and cooperation of other health workers. A whole range of services is needed, but there are priority considerations. Heading the list is nursing service; then economic assistance to patients; and next the establishment of centers where the physician can secure diagnostic services and other facilities to carry on adequate evaluation and treatment.

As captain of the care team, the physician must know the capacities and skills of its members. If he is to have this knowledge, and if he is to learn about patients as people and to understand the emotional and social components in health and disease, there must be a major change in medical education. Postgraduate medical education through medical societies, schools, and special programs, such as those of the American Medical Association and the American Academy of General Practice, is most helpful and needs to be further broadened and extended.

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Of great importance to high quality of medical care is the organizational setting in which the physician works. Isolated doctors working alone are at a disadvantage. Physicians need membership on a hospital staff and the contacts and stimulation of working with other medical practitioners and health workers.

We have not yet capitalized on the possibilities of outpatient services for caring for the chronically ill who do not need institutional care. One of the groups dealing with this subject developed a concept of outpatient services designed to support the family physician by providing specialized diagnostic and consultation services but not undertaking continuing patient responsibility. In this way, the family physician maintains over-all supervision of the case and calls on the outpatient service when needed for highly technical evaluation or treatment service.

The third area of discussion in the Committee on the Patient at Home was home care programs. This group reported that:

"In recent years organized home care programs have taken on great importance in the care of the long-term sick. This is for a variety of reasons. A negative reason is the shortage of hospital beds. The most valid reason is that for suitably selected patients, care in the home, properly organized and delivered, is the best possible care.

"Of importance to the community faced with serious personnel shortages is the value of having family members do tasks for the patient which would otherwise require professional people.

"The essential characteristics of organized home care programs are as follows:

"1. Centralized responsibility for administration;

"2. Coordination of services and resources; and

"3. The development and use of the medical care team to deal with the health needs of the patient and his family. The basic team, as everywhere in the care of the chronically sick, is the doctor, nurse and social worker.

"In home care, the whole range of services needed by the chronically sick can, and if possible should, be provided. Included are such services as dental, nutrition, transportation, medication, and educational services (for home-bound children)."

The Committee on the Patient in an Institution reaffirmed the view that most chronically ill persons need at one time or another the services of a broad range of institutions including general hospitals, chronic disease hospitals or chronic disease units in general hospitals, nursing and convalescent homes, homes for the aged, and mental institutions.

They pointed out a number of procedures and characteristics common to any type of institution which is to give good care to the long-term patient:

1. Before admission to any facility for long-term care the patient needs thorough evaluation by medical and allied personnel. This evaluation includes careful determination of the patient's total situation, and the development of a plan for restoration to maximum social usefulness, and highest possible level of self-sufficiency.
2. Services are individualized to fit the needs of individual patients.

3. The treatment program from the day of admission is geared to the patient's maximum potential of recovery. A spirit of rehabilitation should pervade all services, and permeate the thinking of all personnel.
4. Personnel should be well trained and it is important that they be used at their highest level of competency. There should be a program of personnel education aimed at maximum development of the institution's own staff and, where feasible, the education of new workers entering the health field.

It is important that the general hospital reach out into the community by extending services through home care programs and outpatient services to the patient after he leaves the hospital.

Many detailed improvements must be brought about to make good institutional care of long-term patients generally available. The Committee pointed out three requirements which are of primary importance. Good institutional care of patients with long-term illness will be a reality when:

"Chronically ill patients are fully and frequently evaluated to insure their placement in the most advantageous environment.

"The causes of chronic illness and methods of providing highest quality care are investigated with the same enthusiasm and financial support as are presently applied to other areas of specific endeavor.

"The public conscience no longer tolerates second class care for this sizeable segment of society."

As in all areas of long-term care there is need for more money for institutional care. Equally applicable to long-term patients in and outside institutions is the fact that restoration to maximum vocational usefulness often compensates in dollars for funds expended in rehabilitation. Even where return to employment is impossible, expenditures for rehabilitation often result in attainment of a higher level of self care, reducing a patient's subsequent need for professional and attendant services.

Studies of chronic illness in many cities have revealed literally hundreds of agencies, large and small, offering service of some sort to the patient. Such agencies are rarely effectively coordinated and the result is ineffective service and a confused public.

The Committee on Integration defined its subject as:

"The development of good working relationships between diverse community agencies, facilities, and interests in order to provide better care for the long-term patient. Included in this concept is not only the day-to-day job of helping patients get better care through currently available services and facilities, but also the cooperative development of a well-balanced community program to meet more adequately the needs of a long-term patient."

In brief, we find that much more could be accomplished with the facilities, services, and money now available if they were more efficiently used. Coordination helps greatly in providing the proper service at the proper time, in bringing about early effective treatment and thus helping to prevent permanent disability, and in preventing fractionation of the patient by different specialist interests.

This Committee recommended the provision of special mechanisms, at all levels of government, to coordinate services for the long-term patient in order to ensure proper attention to his special problems.

In local communities such an agency may be constituted by a central service for the chronically ill, a division of a community council, or other administrative device suited to the needs of a particular community. No single pattern can be blueprinted for every community, but experience has shown that specialized counselling and referral services geared to the long-term patient are likely to be more satisfactory than general referral services.

At the state level, there should be a specific public agency to coordinate and develop official programs for care of the long-term patient. Such an agency should also provide consultation and financial assistance to local communities in developing and improving their own services, and should utilize the regional approach to make the resources of urban centers more readily available to rural areas and small communities.

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Education of professional personnel should be further oriented toward coordination, to instill in students a fuller appreciation of the value of teamwork in caring for the long-term patient. The use of medical social workers should be greatly extended among hospitals, health departments, and other health agencies.

Good coordination not only improves the quality of care and the availability of services, but also saves money. Relatively small sums spent on coordination can pay big dividends by preventing costly duplication, permitting full use of expensive skills and facilities, and increasing operating efficiency. Nevertheless, in many jurisdictions there is great difficulty in securing even token investments in coordination.

Funds for coordination should be provided by public as well as private sources in the community, including philanthropic sources, community chests, and voluntary health agencies organized to combat specific diseases. Particularly in the case of state and regional coordinating programs, tax funds may be needed, and should be made available, to supplement voluntary financing.

Pointing to the exceedingly high cost of chronic illness to families, the Research Committee found that we still do not know enough about the cost of chronic illness per se to assess surely what we should do as a nation, or what role states, cities, and voluntary agencies should fill, so that families can avoid the risk of destitution when chronic illness strikes. This gap in knowledge was a barrier to every section of the Conference, not only in assessing needs, but also in evaluating the efficiency of current services and determining how well they meet their stated objectives. Only through research can this ignorance be turned into knowledge which will benefit the long-term patient. Only through research which will define health needs and find better ways of meeting the needs can we apply to care of patients the knowledge we already possess.

Among the recommendations of the Research Committee were these:

> "That every program of care be designed so as to include regular procedures to measure the efficiency and economy with which the service is operated.

"That the effectiveness of every official and voluntary agency in achieving its stated objectives be measured periodically.

"That more research is needed to explore and delineate the community and sociological forces which stimulate or deter effective organization and action in dealing with prolonged illness, and that information on these forces be made more widely available.

"That a continuing agency be established as a focal point for considering problems and stimulating and guiding studies related to services for patients with prolonged illness."

This committee weighed some of the more difficult technical problems involved in designing and conducting research directed to care of the long-term patient. They suggested a number of principles to be followed in any study:

1. Specify clearly the goals of the study.
2. Define terms clearly.
3. Test the research method on a small scale before carrying out a full study.
4. Plan the analysis of data in advance.
5. Set up controls whenever the effect of any action is to be measured.
6. Make sure when the research is planned that the personnel and facilities required for the job will be available.

The Committee on Financing worked from the premise that adequate care for the long-term patient is no longer looked upon as a privilege but should be available to all. Money may be the root of all evil, but it is also the most important single need in the care of the long-term patient. It is the key to development of more trained workers and the provision of more and better facilities.

The committee was of the view that extension of voluntary health insurance is the single most important instrument for financing better care of long-term patients who can afford to pay the basic premiums.

The point was made that "the extent to which voluntary health insurance is now meeting the cost of chronic illness is not a proper measure of its potential effect—even on the unlikely assumption that there will be no further growth in the numbers having health insurance protection or in the adequacy or scope of benefits provided. The people now covered are those who in recent years have met the qualifications for insurance. On the other hand, those who are now suffering from chronic diseases or impairments have, in many instances, become ill or reached advanced age before health insurance was so generally available and so widely purchased. Consequently, the insurance currently in force will furnish much greater protection for the chronically ill of the next generation than can be measured by the benefits received by those now ill."

Supplementary to voluntary health insurance are the benefits derived from private and philanthropic agencies, workmen's compensation, union welfare funds, industrial, agricultural, and professional contributory plans, and others. Where all these fail to meet the needs of adequate care of the long-term

patient for the duration of his illness and his rehabilitation, there is no alternative to the basic proposition that society as a whole, through taxation, must meet the deficit and fill the gap.

The suggestion was advanced that in filling this gap the allocation of tax funds by the state and Federal governments should be based on an equalization principle so that funds made available by the higher level of government would be related to the resources of the political subdivision receiving the funds.

It was the consensus of the Committee that voluntary health insurance and other supplementary instrumentalities must be extended to cover outpatient and home care as well as care in nursing and convalescent homes. Not only will this tend to overcome some of the alleged abuses of hospitalization, but also it will encourage the use of facilities less expensive to maintain and operate than the modern general hospital.

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A recently developed and rapidly expanding form of commercially sponsored voluntary health insurance, that is, major medical expense insurance, was felt to have great potentialities. Major medical expense insurance is a type of accident and sickness insurance specifically designed to solve the problem of how to pay the bills resulting from highly expensive illness. It has been in existence only a few years, but well over a million persons have already acquired such protection. It is available both through individual policies and group insurance, and takes into account virtually all types of medical expenses. Major medical expense policies generally provide for reimbursement above a deductible amount ranging from $100 to $500. Maximum benefits range from $2,500 to $10,000. In some group policies, if the illness is chronic, the maximum amount may be paid again and again in successive years for the same illness. In policies of this nature, the deductible provisions apply anew each year. Ordinarily the insured pays 20 to 25 per cent of the expenses above the deductible amount and below the maximum, thus being a "coinsurer" to that extent.

The Committee on Financing examined the proposed legislation on health insurance prepayment plans (S.3114, the bill which carries the "reinsurance" proposal). The consensus was that the bill represents a step in the right direction. However, the Committee's conclusion was that the proposed reinsurance program has many practical limitations and will not in itself serve as a substantial influence in solving the problem of long-term care.

The Finance Committee emphasized the great importance of rehabilitation. It was pointed out that more effective and more widely available rehabilitation services would in the long run reduce the cost of care of the long-term patient.

The opinion was expressed that the multiplicity of sources of care and the limitation on the use of funds by categorizing of individuals by age and diagnosis result in overlapping services, gaps in service, and sometimes the failure to provide the type of service best suited to the individual's need.

In regard to public financing it was concluded that the amount of care and its quality could be improved with the same amount of money now being spent if programs were more carefully planned and better coordinated.

As for financing facilities for the care of the long-term patient and capital expenditures for that purpose, it was generally agreed that private resources and

government, Federal, state, and local, could each participate to the advantage of all. The Committee pointed out that extension of the Hospital Survey and Construction Act* as proposed by the President will stimulate the construction of chronic disease hospitals, nursing homes, and special rehabilitation and diagnostic facilities.

In the months which have elapsed since the 1954 Conference, the Commission on Chronic Illness has had some opportunity to study in detail the material produced at Chicago and to relate it to that which had already been prepared by the pre-Conference study groups.

The Commission's job now is to get this material into its most usable form, and with as little delay as possible. To that end, an editorial committee composed of five members of the Commission is working closely with the Commission staff. The report will draw heavily on the pre-Conference study group reports as well as the committee reports made to the Conference.

Finally, with the report as a basis, it should be possible for the Commission to formulate a group of recommendations and set forth principles which will be useful to the thousands in the health and allied professions who are working to improve the care of the long-term patient.

*Subsequent to the Conference the extension of the Hospital Construction Act was accomplished when Public Law No. 482 was passed by Congress and signed by the President.

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Review

INFLUENCE OF SEX AND SEX HORMONES UPON THE DEVELOPMENT OF ATHEROSCLEROSIS AND UPON THE LIPOPROTEINS OF PLASMA

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ONE of the challenging problems concerning atherosclerosis is the influence of sex upon its incidence, progress, and complications. Clinical experience indicates that men are more susceptible to its development and that women, particularly young women, possess some degree of protection from its more serious complications. Efforts have been made to define anatomic or chemical peculiarities of the sexes which might contribute to a greater consequence of the disease in man. Many detailed studies have been undertaken concerning conditions in the domestic fowl, the only conveniently available vertebrate other than man that is known to have a high incidence of spontaneous atherosclerosis. The effects of gonadal hormones have been extensively tested both in man and in the chick with the purpose of determining whether these specific chemical substances favor or inhibit atherogenesis.

Search for evidence on the influence of sex has spread from clinical observations and studies of comparative anatomy to detailed considerations of chemical pathology. The resulting investigations have thrown some light not only on the genesis of lipid deposits in the arterial wall but also on the nature and significance of protein-lipid relationships in plasma. In the following discussion an attempt will be made to examine some of the scattered, incomplete, and often conflicting information.

I. INFLUENCE OF SEX ON THE DEVELOPMENT OF HUMAN ATHEROSCLEROSIS

A. *On the Extent of Atheromatous Deposit.*—Atherosclerosis is extremely prevalent in human adults of both sexes. Estimates of its incidence vary widely with the criteria used for its recognition. Inclusion of statistics of cases showing only yellowish discoloration of the intima with streaks of lipid but without intimal thickening has led some authors[1,2] to the conclusion that all of mankind after 6 months of age exhibit stigmas of atherosclerosis. When such minor lesions

are ignored and the appearance of fat deposit with intimal thickening is taken as the first evidence of the disease, the frequency of atherosclerosis has been variously estimated. Sjövall and Wihman[3] were able to demonstrate patches of atheroma in less than 5 per cent of individuals during the first two decades, in 10 per cent or less during the third decade, but close to 25 per cent in the period between the ages of 30 and 39. Employing less well-defined criteria, Willius, Smith, and Sprague[4] thought that they could detect lipid deposits in more than 20 per cent of individuals under the age of 10, and in about 80 per cent of patients in the second decade. Wilens[5] has found that by the age of 50, more than one-half the population display gross lesions, and that of those who die after 75, 85 per cent are afflicted with moderate or advanced atherosclerosis.

A high incidence in both men and women has been known for more than one century. Hasse[6] in 1841 stated that sex had no significant influence. He did note, however, that lesions developed in women at a later age and seldom appeared in so extensive a form. He also found that in men the coronary arteries and the vessels of the lower extremities were more affected, but that in women the abdominal aorta showed greater involvement. Rokitansky[7] believed that sex caused no significant difference in the incidence of lipid infiltration although he agreed with Hasse that in women the involvement of the abdominal aorta was more extensive.

Willius, Smith, and Sprague[4] found only the slightest differences between the sexes. In the first decade the disease was detected in 22 per cent of the girls and 24 per cent of the boys, in the second decade in 79 per cent of girls and 80 per cent of boys.

The situation as it existed in Sweden in 1934 was well shown in the detailed study of Sjövall and Wihman,[3] who analyzed post-mortem observations of 1,075 individuals from Stockholm and 305 from Lund. The authors thought that this material permitted some comparison of the conditions of urban and rural life.

Estimate of total atherosclerotic involvement was based on separate analysis of conditions in four parts of the aorta, in the three principal coronary vessels, in the celiac, splenic, mesenteric, femoral, subclavian, and pulmonary arteries. The results are indicated in Table I.

TABLE I. EXTENT OF TOTAL ATHEROSCLEROSIS IN MALES AND FEMALES AT VARIOUS AGES. VALUES ARE EXPRESSED AS INDICES DERIVED BY COMBINING SEPARATE OBSERVATIONS ON THE AORTA AND ITS MAIN BRANCHES (SJÖVALL AND WIHMAN[3])

AGE (YR.)	STOCKHOLM		LUND	
	MEN	WOMEN	MEN	WOMEN
1-20	0.3	0.5	0	0.2
21-30	1.3	1.2	0.6	0.5
31-40	3.5	2.3	2.7	1.9
41-50	8.0	5.6	3.5	5.0
51-60	10.5	10.0	8.4	9.3
61-70	15.7	13.3	13.0	15.0
71-80	16.6	18.5	19.0	23.0
81-90	21.7	20.0	20.8	25.5

In the group from Stockholm the extent of atherosclerosis was slightly greater in the men, but in the hard-working, well-nourished farm laborers of Lund the women showed slightly more atherosclerosis than did men at all ages except for the period of the fourth decade.

Separate analyses of the degree of involvement in the aorta and most of its main branches revealed variable but inconsequential differences in the sexes. In several instances the women exhibited slightly more atherosclerosis. The abdominal aorta, which was the most frequent site of atheroma, was more involved in the women of Stockholm during the seventh and eighth decades, and in the women of Lund at all ages. Men from Stockholm had much more atherosclerosis in the femoral arteries while those from Lund had slightly less than did the women.

The most significant differences attributable to sex appeared in the examination of the coronary arteries. These are shown in Table II.

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TABLE II. EXTENT OF ATHEROSCLEROSIS IN CORONARY ARTERIES OF MALES AND FEMALES AT VARIOUS AGES. VALUES ARE EXPRESSED AS INDICES DERIVED BY COMBINING SEPARATE OBSERVATIONS ON INDIVIDUALS OF THE GROUP (SJÖVALL AND WIHMAN[3])

AGE (YR.)	RT. CORONARY ARTERY		LT. DESCENDING CORONARY ARTERY		LT. CIRCUMFLEX CORONARY ARTERY	
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
Stockholm						
1-20	0	0	0	0	0	0
21-30	0	0	0.2	0.2	0.1	0
31-40	0.3	0.2	0.3	0.3	0.2	0.2
41-50	0.6	0.4	1.0	0.6	0.5	0.4
51-60	0.9	0.9	1.2	1.0	0.7	0.6
61-70	1.3	1.1	1.5	1.3	1.1	0.9
71-80	1.3	1.2	1.6	1.5	1.1	1.2
81-90	1.7	1.4	1.9	1.8	1.6	1.3
	6.1	5.2	7.7	6.7	5.3	4.6
Lund						
1-20	0	0	0	0	0	0
21-30	0.1	0	0.1	0	0.1	0
31-40	0.2	0.2	0.4	0.3	0.3	0.2
41-50	0.6	0.5	0.6	0.5	0.6	0.5
51-60	0.8	0.8	0.9	0.8	0.9	0.8
61-70	1.2	1.0	1.3	1.2	1.2	1.1
71-80	1.3	1.7	1.4	1.7	1.4	1.7
81-90	1.4	2.0	1.6	2.0	1.6	2.0
	5.6	6.2	6.3	6.5	6.1	6.3

In both groups, atherosclerosis of the coronary vessels appeared at an earlier age in men. This was notable in the men from Stockholm after the fourth

decade. It was still more evident in the men of Lund, whose other arteries often showed less involvement than did those of the women.

The observations of Sjövall and Wihman deserve detailed attention because of their thoroughness and because they include examinations of many vessels in every decade. Later investigations tend to support them.

Wilens[5] reported on the extent of general atherosclerosis as revealed by autopsies on 798 men and 452 women at Bellevue Hospital in New York City. Although his statistics were based on unmodified subjective impressions of many pathologists over a period of several years, they serve as an approximate index of the influence of sex on the development of atherosclerosis in a miscellaneous group of patients over the age of 35.

The extent of atherosclerosis tended to be slightly greater in men but the differences were not great, and there was little indication that women were effectively protected at any period from the development of lipid deposits.

Boas and Epstein[8] attempted to estimate during life the degree of involvement of the aorta in a group at the Sidney Hillman Health Center in New York City. Such an appraisal is admittedly difficult because atherosclerosis in this location does not often lead to recognizable symptoms, and the extent or even the presence of the disease can only be inferred by x-ray demonstration of calcification in the vessel walls. By this criterion there was some evidence of atherosclerosis in 25.5 per cent of 343 men at an average age of 59.8 years and 22.7 per cent of 225 women at an average age of 54.

Another study of the influence of sex on the extent of atherosclerosis in coronary vessels was made by Ackerman, Dry, and Edwards,[9] who studied 600 hearts from relatively unselected autopsies in women ranging in age from 30 to 89 and compared them with an almost precisely similar series of 600 men studied by White, Edwards, and Dry.[10] The degree of atherosclerosis was estimated in each of 16 locations in the coronary vessels of each heart. Values for total degree of involvement derived by combining all observations are presented in Table III.

TABLE III. EXTENT OF CORONARY ATHEROSCLEROSIS IN MALES AND FEMALES AT VARIOUS AGES. VALUES ARE INDICES DERIVED BY COMBINING OBSERVATIONS IN SEVERAL LOCATIONS IN ALL INDIVIDUALS OF THE GROUPS (ACKERMAN, DRY, AND EDWARDS[9])

SUBJECTS	AGE (YR.)					
	30-39	40-49	50-59	60-69	70-79	80-89
Men	1.56	1.74	2.46	2.21	2.32	2.29
Women	1.13	1.30	1.48	1.69	1.99	2.03

Their results, in accord with those of Sjövall and Wihman, indicate an earlier development of coronary atherosclerosis in men. Women in the sixth decade have about the same degree of involvement as men in the fourth; in the seventh decade their involvement corresponds to that of men in the fifth. They

do not attain, even in old age, the advanced degree of sclerosis exhibited by men during the sixth decade. It is worthy of note that in women the extent of involvement increases steadily with age, and there is no indication that the menopause is followed by any abrupt augmentation of lipid deposit. It is of no less interest that even in the ages from 30 to 39 the degree of coronary atherosclerosis of women is more than 70 per cent of that of men.

B. *On the Clinical and Pathologic Complications of Coronary Heart Disease.*—Atherosclerotic narrowing and occlusions of the main coronary arteries and their primary branches form the basis of more than 90 per cent of the cases of angina pectoris and myocardial infarction.[11-13] Other causes are rare.[14,15] It might be expected, therefore, that the incidence of the complications of coronary heart disease would be directly proportional to the degree of the atherosclerosis of the vessels. It appears, however, that this presumption can be only approximately correct, for the sex differences in the degree of atheroma disclosed in the preceding survey while definite are insufficient to permit prediction of the tremendously greater frequency of coronary heart disease in men.

Clinically, coronary thrombosis and myocardial infarction occur from 5 to 10 times as often in men as in women.[8,16-18] Under the age of 40, predominance of the incidence in males is 25 to 1 or more.[19,20] Statistically, the death rate of males from coronary artery disease is higher in every age group.[21,22] In sudden death from coronary artery disease, Rabson and Helpern[13] found in New York City only 6 per cent of 617 cases in women. In Hallermann's[23] series of 486 cases, women constituted 25 per cent of the total and had a greater incidence than did men in the eighth and ninth decades. Between the ages of 51 and 60, however, there were 122 men and 17 women.

TABLE IV. INCIDENCE OF CORONARY ARTERY OCCLUSION IN MEN AND WOMEN AT VARYING AGES (SCHLESINGER AND ZOLL[24])

AGE (YR.)	SEX	TOTAL NUMBER OF HEARTS	HEARTS WITH OCCLUSIONS	
			NUMBER	PER CENT
20-39	M	44	1	2.3
	F	19	1	5.3
40-59	M	85	20	23.5
	F	56	2	3.6
60-79	M	115	43	37.4
	F	65	21	32.3
80 on	M	9	4	44.4
	F	7	2	28.6
Total		400	94	23.5

The most decisive evidence of a greater incidence of coronary heart disease in men is afforded by the observations of Schlesinger and Zoll,[24] the results of whose injections and dissections of coronary arteries are presented in Table IV.

In every age group occlusions were more frequent in men. Between 40 and 59 the incidence was more than 6 times as great in men.

Sex differences in the incidence of coronary heart disease which are so evident in the general population may be almost entirely obliterated in the presence of strongly atherogenic diseases; such as, diabetes, familial hypercholesterolemic xanthomatosis, and nephrosis.

In diabetes of long standing, atherosclerosis is almost universal. Among 484 autopsies of diabetic persons who were known to have the disease for five years or more, Warren[25] had seen or heard of only 4 who had no evidence of atherosclerosis. In the injections of coronary arteries of 50 diabetic patients by Stearns, Schlesinger, and Rudy,[26] significant coronary artery disease was found in 75 per cent. Among diabetic women over the age of 40 the incidence of significant coronary atherosclerosis, angina pectoris, and death due to coronary heart disease was as great as among diabetic men. This has been the experience of other observers.[27-30] Clawson and Bell[31] were able to show that also in the period below the age of 40 the incidence of fatal coronary occlusion was the same in females as in males.

In case records of familial hypercholesterolemic xanthomatosis, there are many isolated examples of coronary disease in girls and young women.[32-36] The observations of Adlersberg, Parets, and Boas[37] indicate that girls who have inherited a xanthomatous tendency have a high incidence of coronary heart disease but are somewhat protected by their sex from its serious consequences. Of 46 males under the age of 40, 23.9 per cent exhibited evidence of coronary heart disease, while in 31 women of similar age the incidence was only 12.9 per cent.

The influence of sex on the development of coronary heart disease in the nephrotic syndrome has not been specifically studied. Lipid deposits have been found in the aorta and coronary arteries at ages ranging from 4 to 29.[38,39] Many of Steiner and Domanski's[40] 54 youthful patients with glomerulonephritis had hypercholesterolemia of a degree indicative of the nephrotic syndrome. In 52 of them who died between the ages of 1 and 39, there was gross aortic atherosclerosis, while 70 per cent of the group showed lipid infiltration of the coronary arteries. Controls consisting of individuals of comparable age and sex showed only 35 per cent incidence of aortic atherosclerosis and 19 per cent of coronary disease. Steiner and Domanski made no detailed analysis of the sex of their patients. Since, however, many of them were females and all but 2 of the group developed atherosclerosis, it is apparent that sex exercised no effective control on lipid deposit under the potent atherogenic conditions of the nephrotic syndrome.

C. *On the Clinical and Pathologic Complications of Peripheral Vascular Disease.*—Pathologic studies of involvement of the arteries of the extremities are unsatisfactory because of the rarity of even perfunctory examination of these vessels at autopsy. The recently developed injection technique of Wessler and Scheslinger,[41] which might afford greater information, has not as yet been applied to the study of large groups. Information concerning the extent of involvement

is derived chiefly from examination of the femoral arteries, as in the study of Sjövall and Wihman,[3] or from the dissection of amputated limbs.[42] Estimates of the influence of sex are dependent chiefly on clinical studies of the complications of atherosclerosis of the peripheral vessels.

Observations of Hines and Barker[43] indicate that the incidence of peripheral vascular disease is about 6 times as great in men as in women. Serious complications are rare in either sex before the age of 40. Boas and Epstein[8] found 3.8 per cent of 343 men and 0.9 per cent of 225 women, all over the age of 40, with some evidence of peripheral atherosclerosis.

Evaluation of the incidence in men and women is difficult because of difference in their occupations and physical activities. The study of Lake, Pratt, and Wright[44] is therefore especially valuable, since it is concerned with employees of a large department store where many of the men and women were engaged in essentially similar occupations over periods of several years. Judgment of the presence and extent of atherosclerosis was based on history, physical signs, oscillometric studies, and roentgenologic evidence of calcium in the arteries of the legs. The radiologic examinations accounted for most of the diagnoses. Since many of the cases with demonstrable calcification of vessels were asymptomatic, the statistics of Lake, Pratt, and Wright cannot be compared directly with those of Hines and Barker. As indicated in Table V, they show a greater incidence of arterial involvement in men. The predominance of males in the entire group is 2.3:1.0; in the fifth decade 3.4:1.0; and in the group above 60 only 1.4:1.0. In general, it appears that the calcification develops about 10 years later in women. Further examination of the data shows that 30 per cent of men but only 12 per cent of women have calcification which the authors could classify as 3+ or 4+.

TABLE V. INCIDENCE OF ATHEROSCLEROTIC INVOLVEMENT OF ARTERIES OF THE LOWER EXTREMITIES IN MEN AND WOMEN (LAKE, PRATT, AND WRIGHT[44])

SUBJECTS	PERCENTAGE OF ARTERIAL INVOLVEMENT			
	AGED 40-49	AGED 50-59	AGED 60 AND OVER	TOTAL
Men	27	55	77	46
Women	8	26	56	20

D. *Anatomic Factors That May Contribute to the Greater Consequence of Atherosclerosis in Men.*—Since in man the greater susceptibility to the complications of atherosclerosis is most evident in the arteries of the coronary system and of the lower extremities, search for sex-linked local factors within these vessels is appropriate. Dock[45,46] emphasized the influence of the thickness of the intima in the selective location of atheroma and recalled the observations of older workers[47,48] that relatively few arteries show, from birth to advanced age, intimal thickening comparable to that seen in the epicardial parts of the coronary

system. In a study of 12 infants of each sex who died within twenty-four hours of birth, Dock[45] found a greater frequency and degree of intimal thickening in the male children. Lansing[49] was unable to demonstrate any sex differences in the thickness of intima of the coronary arteries of infants at birth. Fangman and Hellwig[50] found thickening of the intimal layer of the coronary arteries in 8 of 15 males but in only 4 of 15 females. Minkowski[51] studied the intima in the coronary vessels in 122 males and 82 females who had died at or soon after birth. In the whole group he could demonstrate no significant sex difference. His material was, however, more miscellaneous than that of Dock or of Fangman and Hellwig. When he studied a subgroup consisting of 51 males and 25 females whose deaths occurred within twenty-four hours of birth and could be attributed to birth trauma or asphyxia, he was able to show significantly greater thickness of intima in males. Lober,[52] in a study of the coronary vessels, found greater atherosclerotic involvement in males at all ages. The difference between the sexes during the first decade, however, was not statistically significant. During the first month of life it was very small. In the male infant the intima constituted 15 per cent of the total thickness of the coronary artery; in the female it was 12 per cent.

In spite of the somewhat conflicting evidence, it appears that intimal thickness of the coronary vessels may be more frequent and of greater degree in male infants at birth. No adequate data have been accumulated concerning the development of the arteries in the two sexes during subsequent years. The possibility of a local anatomic cause for the greater incidence of atherosclerotic complications in men must be given full consideration. As Dock[45] himself pointed out, however, even very marked thickening of the arterial intima is not sufficient to cause atherosclerosis in vessels that are not subject to other atherogenic factors.

E. *Chemical Factors That May Contribute to the Greater Consequence of Atherosclerosis in Men.*—The range of concentration of cholesterol and phospholipid in plasma is the same in males and females.[53] Studies by many investigators have failed to demonstrate any sex-linked differences[54-57] The range of concentration of total lipid is also unmodified by the sex of the subjects.[56-58]

Differences between the lipid composition of the plasma of men and women have been detected, however, by applying the methods of chemical fractionation, electrophoresis, and ultracentrifugation to the study of the concentration and distribution of lipoproteins in plasma.

By the use of Cohn's method #10[59] for protein fractionation, Russ, Eder, and Barr[60] studied the distribution of lipoproteins in the plasma of 85 normal persons. Analyses were made of protein, cholesterol, and phospholipids in the unfractionated plasma and in each of the several fractions. Sex-linked differences were apparent in a group of young individuals but were not demonstrable in older men and women. Results are summarized in Table VI.

Russ, Eder, and Barr did not determine the lipoproteins directly. Their analyses were concerned only with the amounts of lipid recovered in the several protein fractions. Cohn and his co-workers[59,61,62] had shown, however, that all of the lipids of plasma can be recovered in the fractions indicated in Table VI,

that the lipids contained in Fraction IV+V+VI are combined with $alpha_1$ globulins in the form of alpha lipoproteins, and that those in Fraction I+III are bound to $beta_1$ globulin in the form of beta lipoproteins. They also gained considerable information concerning the composition of the two types of protein. The results of some of their analyses are shown in Table VII.[63]

TABLE VI. DISTRIBUTION OF CHOLESTEROL IN MEN AND WOMEN AT VARYING AGES (RUSS, EDER, AND BARR[60])

SUBJECTS	AGE (YR.)	CHOLESTEROL IN PLASMA (MG. PER 100 ML.)	CHOLESTEROL IN COHN FRACTION IV + V + VI		CHOLESTEROL IN COHN FRACTION I + III	
			% OF TOTAL	MG. PER 100 ML.	% OF TOTAL	MG. PER 100 ML.
Women	18-35	187	34.3	64	61.8	116
Men	18-35	197	25.2	50	72.0	142
Women	45-65	252	23.4	59	75.0	189
Men	45-65	239	22.9	55	75.3	180

TABLE VII. COMPOSITION OF LIPOPROTEINS. FAT VALUES FOR ALPHA LIPOPROTEIN ARE FROM ANALYSES BY DR. ROBERT ROSENBERG OF FRACTION IV-1,1 FROM NORMAL HUMAN PLASMA.[63] VALUES FOR BETA LIPOPROTEIN ARE FROM ANALYSES OF ONCLEY, GURD, AND MELIN[61]

LIPOPROTEIN	PER CENT COMPOSITION		
	CHOLESTEROL	PHOSPHOLIPID	PEPTIDE
$Alpha_1$	12.0	21.0	57
$Beta_1$	30.9	29.3	23

The values in Table VII must be regarded as tentative and approximate, not only because the analyses were made on specimens obtained under special conditions, but also because each type of lipoprotein recovered in the Cohn fractions is probably composed of several distinct substances of somewhat variable composition. They may be used, however, to calculate the approximate amounts of lipoproteins implied by the lipid analyses of Russ, Eder, and Barr. In Table VIII the results of such calculations are shown.

Differences between young men and women similar to those shown by Russ, Eder, and Barr have been obtained by Nikkilä[64] and by Antonini[65] with the method of paper electrophoresis. Nikkilä found by analysis of cholesterol and phospholipid in segments of paper strips that men in the age group below 40 have a significantly larger proportion of their total cholesterol in the form of beta lipoprotein and a correspondingly smaller amount in the form of alpha lipoprotein. After the age of 40 the values in men and women are approximately

equal. Antonini showed that the beta lipoprotein–alpha lipoprotein ratios are definitely higher in men. His absolute values for the ratios do not correspond closely to those calculated from the data of Russ, Eder, and Barr, but the differences between the sexes are of the same order.

TABLE VIII. ALPHA LIPOPROTEIN, BETA LIPOPROTEIN, AND BETA LIPOPROTEIN–ALPHA LIPOPROTEIN RATIOS IN HEALTHY YOUNG MEN AND WOMEN CALCULATED FROM DATA OF RUSS, EDER, AND BARR.[60] VALUES FOR ALPHA LIPOPROTEIN ARE OBTAINED BY DIVIDING CHOLESTEROL CONCENTRATION IN FRACTION IV + V + VI BY 0.12. VALUES FOR BETA LIPOPROTEIN ARE CALCULATED BY DIVIDING CHOLESTEROL CONCENTRATION IN FRACTION I + II + III BY 0.309

SUBJECTS	TOTAL CHOLESTEROL (MG. PER 100 ML.)	CHOLESTEROL IN IV + V + VI (MG. PER 100 ML.)	ALPHA LIPOPROTEIN (MG. PER 100 ML.)	CHOLESTEROL IN I + II + III (MG. PER 100 ML.)	BETA LIPOPROTEIN (MG. PER 100 ML.)	BETA / ALPHA RATIO
Healthy women (Aged 18-35)	187	66	533	123	399	0.75
Healthy men (Aged 18-35)	197	50	417	147	477	1.15

Other evidence of sex-linked variations in lipoprotein composition of plasma has come from use of the ultracentrifuge. Observations of Jones and his colleagues[66] with Gofman's technique[67] for the study of low-density lipoproteins have shown that lipoproteins designated by them in terms of Svedberg flotation units as S_f 10—20 or 12—20 have on the average a higher concentration in the serum of young men. They found that 20 per cent of the men but only 2 per cent of the women between the ages of 31 and 40 have over 60 mg. per 100 ml. of the S_f 10—20 lipoproteins. Similar differences could not be demonstrated in older age groups. Men and women in the sixth decade have about equal concentrations.

Gofman's method is so adjusted that it does not permit observations on the alpha lipoproteins. Lewis and Page[68] have, however, devised a method by which both alpha and beta lipoproteins may be studied in the ultracentrifuge. They have been able to show that below the age of 40, men have on the average relatively higher concentrations of beta lipoproteins and correspondingly lower alpha lipoproteins.[69,70]

The essential conformity of results from three methods so different as chemical fractionation, electrophoresis, and ultracentrifugation lends much weight to the assumption that the lipoprotein complexes which they measure are components of the native serum and not simply artefacts, and that a significant difference in their relative amounts characterizes the plasma of young men and women.

Other sex-linked differences have been disclosed since the discovery that the injection of heparin will cause rapid disappearance of postprandial hyperlipemia[71] and chylomicronemia.[72] The phenomenon and its mechanism have been extensively studied by many observers.[73-76] The rate of clearing has been found to

vary in individuals and in groups. Block, Barker, and Mann[77] have shown that it is more rapid in young women than in young men. In 20 women aged 19 to 42, there was excellent clearing, averaging 85 per cent with a range of 62 to 100 per cent fifteen minutes after injection of heparin and three hours after ingestion of the fat meal. A group of 23 men aged 27 to 46 who were studied under identical conditions averaged 74 per cent, clearing with a range of 28 to 100 per cent. Two of the young men had clearing values of less than 40 per cent.

Still another sex distinction has recently become apparent. Mast cells have been found in greater number in young women than in young men by Hellström and Holmgren[78] and more recently by Constantinides[79] and by Cairns and Constantinides.[80] This is of some possible importance because of the supposed function of the mast cells in the production of heparin or heparinoid substances.[81]

F. *Relationship of Sex-Linked Chemical Differences to the Pathogenesis of Atherosclerosis.*—In patients who have survived myocardial infarction and who may be fairly regarded as atherosclerotic, the distribution of lipoprotein deviates from that of normal young women in a manner which represents an exaggeration of the differences encountered in young men and in older men and women.

By the Cohn method of protein fractionation it was shown by Barr, Russ, and Eder[82] that the concentration of beta lipoproteins is relatively increased and that of alpha lipoproteins is correspondingly diminished. Similar abnormalities have been shown by Swahn,[58] Nikkilä,[64] and Antonini[65] using the method of paper electrophoresis, and by Lewis and Page[70] with a combination of the methods of ultracentrifugation and electrophoresis. In the same type of patients Gofman and his associates[66,83,84] have shown an average concentration of S_f 10—20 lipoproteins considerably greater than normal.

In diseases such as familial hypercholesterolemic xanthomatosis, nephrosis, and in many cases of diabetes, all of these deviations from normal are considerably exaggerated.[82,84]

It has also been shown that those who are known to have advanced atherosclerosis have a less than normal concentration of heparin or heparinoid substances in the circulating blood,[65] that the number of tissue mast cells are abnormally diminished,[78,80] and that the clearing of postprandial hyperlipemia by heparin is abnormally delayed.[77]

The relationship of the state of lipoprotein concentration and distribution to the tendency or lack of tendency to the deposit of lipids in arteries can be indicated by the data obtained from electrophoresis or ultracentrifugation. It has been shown with greater clarity from the results of Cohn microfractionation of plasma.[85] In Table IX, data from Cohn fractionation together with calculated values for lipoproteins and the beta lipoprotein–alpha lipoprotein ratios are shown for a number of situations in which the atherogenic tendency differs greatly. Only a few groups have been chosen for presentation: normal dogs in which there is essentially no spontaneous atheroma and in which experimental atherosclerosis is accomplished with difficulty; young women in whom coronary heart disease is rare; young men in whom atherosclerotic complications are more frequent; survivors of myocardial infarction where the damage of atheroma is already apparent; patients with familial xanthomatosis in whom the atherogenic

tendency is maximal; and finally dogs made atherosclerotic by the method of Bevans, Davidson, and Abell,[86] in which both thiouracil and cholesterol are fed.

TABLE IX. DATA FROM COHN FRACTIONATION OF PLASMA WITH CALCULATION OF CONCENTRATION OF LIPOPROTEINS AND BETA LIPOPROTEIN–ALPHA LIPOPROTEIN RATIOS IN A NUMBER OF CONDITIONS OF WIDELY VARIANT ATHEROGENICITY. DATA ARE ADAPTED FROM BARR.[85] VALUES FOR LIPOPROTEINS ARE CALCULATED AS IN TABLE VIII

SUBJECTS	TOTAL CHOLESTEROL (MG. PER 100 ML.)	PER CENT TOTAL CHOLESTEROL IN FRACTION I + II + III	BETA LIPOPROTEIN (CALC.) (MG. PER 100 ML.)	BETA LIPOPROTEIN / ALPHA LIPOPROTEIN RATIO
Normal dogs	167	17.1	92	0.08
Healthy women (Aged 18-35)	187	65.7	399	0.75
Healthy men (Aged 18-35)	197	74.8	477	1.15
Survivors of myocardial infarction	258	85.9	718	2.39
Familial xanthomatosis	459	92.9	1,380	6.65
Atherosclerotic dogs	2,698	94.2	8,240	6.39

The evidence is convincing that there is a correlation between atherogenicity and the variations in chemical composition of the plasma. It is also apparent that the pattern of lipids in the plasma of young women is such as might be expected to afford some degree of protection. The data, however, cannot be used as proof that the relative freedom of young women from coronary and peripheral vascular disease is dependent upon the chemical constitution of the blood.

II. INFLUENCE OF SEX ON ATHEROSCLEROSIS IN THE DOMESTIC FOWL

A. *On the Development of Spontaneous Atherosclerosis.*—Since mammals other than man seldom develop spontaneous atherosclerosis and since many birds have a high incidence,[87,88] the domestic fowl has been selected as a convenient experimental subject.[89,90]

The spontaneous lesions of the arteries have been examined carefully by Dauber,[91] and by Chaikoff, Lindsay, Lorenz, and Entenman.[92] Early in the life of the rooster and in the immature female, elevated, smooth, longitudinal, ridge-like thickenings develop in the abdominal aorta. Such lesions have not been observed in the ascending aorta and arch or in the coronary arteries. In cockerels commercially fattened for market, lipid and cholesterol could be demonstrated in the lesions of the abdominal aorta. In cockerels reared in the laboratory throughout life on a mash devoid of cholesterol supplement, the thickened ridges of the abdominal aorta contained no demonstrable lipid.[93] A justifiable question may be raised as to whether this intimal thickening of the rooster and the immature pullet is a true atherosclerotic lesion.

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In the female birds at puberty and during the egg-laying period, there are much more extensive arterial changes. Nodular, ridgelike plaques in the descending thoracic and abdominal aortas are infiltrated with lipids which may be demonstrable by gross as well as microscopic examination. The ascending aorta and the aortic arch may be streaked with deposits of yellow fat. The involved area is smooth, and no fibrosis or true atheroma is evident. The change is limited to diffuse accumulation of lipid in the intima and media. Neither lipid-bearing foam cells nor cholesterol crystal clefts are readily demonstrable. No coronary lesions which are recognizably atherosclerotic can be shown in the spontaneous atherosclerosis of the domestic fowl either in the rooster or in the laying hen. Again the question must be asked whether this spontaneous deposit of fat in the laying hen is closely analogous to human atherosclerosis.

B. *On the Lipid Composition of the Blood.*—Chemical differences in the sexes in birds have been known since 1916[94] and were studied by a number of investigators.[95-98] In the cockerel, mature rooster, and the pullet before puberty the cholesterol concentrations and the cholesterol-phospholipid ratios of the plasma are low; the total lipid is approximately at the level found in human plasma. No significant differences in the levels of cholesterol, phospholipids, or total fatty acids of the blood of male birds examined at various age periods ranging from 71 to 276 days are demonstrated.[92,97,98]

In the female bird at puberty and in hens during the laying period, changes occur in the lipid composition of the plasma that have no counterpart in human physiology. The total concentration in the plasma is greatly increased and may attain levels of more than 4,500 mg. per 100 ml. This is chiefly attributable to the accumulation of neutral fat, less to changes in phospholipids, and least to increase in the concentrations of cholesterol. The cholesterol-phospholipid ratios are much lower than in the male or immature female bird. It is remarkable that there is almost no increase in esterified cholesterol.

The conditions in roosters, immature females, and laying hens as found by Lorenz, Entenman, and Chaikoff[97] are shown in Table X.

TABLE X. INFLUENCE OF SEX ON THE LIPID COMPOSITION OF THE DOMESTIC FOWL (LORENZ, ENTENMAN, AND CHAIKOFF[97])

SUBJECTS	CHOLESTEROL		PHOSPHOLIPIDS (MG. PER 100 ML.)	TOTAL LIPID (ML. PER 100 ML.)
	TOTAL (MG. PER 100 ML.)	FREE (MG. PER 100 ML.)		
Males	114	92	299	428
Immature females	117	83	282	466
Laying hens	125	109	642	1,689

The changes encountered in the female bird are found during puberty and before egg-laying has commenced; they are not dependent upon the duration

or intensity of egg production or the level of dietary fat. Enormous concentrations of lipid appear in laying birds on low-fat diets, although the neutral fat and free cholesterol tend to be higher with greater intake of ingested fat.

Observations on the distribution and concentration of lipoproteins in spontaneous atherosclerosis of the chick are not at present available.

C. *The Effect of the Administration of Estrogen on the Lipid Composition of the Blood and on the Development of Atherosclerosis.*—In 1940, Entenman, Lorenz, and Chaikoff[99] reported the effects of crystalline estrogens on the blood lipids of the birds. Anatomically and chemically, the changes produced by the estrogens both in cockerels and in immature females resemble the alterations exhibited by the pullet at puberty. The concentrations of cholesterol, phospholipid, and neutral fat greatly increased. The atherosclerotic changes in the vessels corresponded quite precisely to those previously observed at puberty. The nature and extent of changes are indicated in Table XI.

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TABLE XI. EFFECT OF ADMINISTRATION OF ESTRONE IN THE CHICK (ENTENMAN, LORENZ, AND CHAIKOFF[99])

SEX	NUMBER OF BIRDS	RANGE	CHOLESTEROL		PHOSPHOLIPIDS (MG. PER 100 ML.)	TOTAL LIPIDS (MG. PER 100 ML.)
			TOTAL (MG. PER 100 ML.)	FREE (MG. PER 100 ML.)		
Controls						
Male	8	Maximum	132	77	330	487
		Minimum	87	50	225	344
		Mean	109	69	279	415
Female	7	Maximum	138	93	316	455
		Minimum	90	62	197	314
		Mean	106	78	253	385
Estrone Treated						
Male	4	Maximum	207	138	543	1,340
		Minimum	150	101	440	764
		Mean	190	116	498	1,112
Female	4	Maximum	137	118	713	848
		Minimum	112	64	297	527
		Mean	129	95	525	755

When the estrogen is given for a longer period, as in the experiments of Chaikoff, Lindsay, Lorenz, and Entenman,[92] the changes may be much greater, with values for total lipids as high as 17,100 mg. per 100 ml.; for phospholipid as high as 5,200 mg. per 100 ml.; and for cholesterol as high as 885 mg. per 100 ml.

The arterial changes which result in cockerels and in immature female chicks following the administration of estrogens may mimic precisely those shown

in the untreated mature laying hen.[92,100] Stamler and Katz[101] saw typical atheromas with fibroblastic thickening, foam cells of the macrophage type, lipid-bearing fibroblasts, extracellular fat droplets, and cholesterol crystals and clefts. Involvement of the coronary arteries is limited to microscopic accumulations of lipid in the media.[102]

D. *Cholesterol-Induced Atherosclerosis in Chicks.*—Extensive observations have been made on the arterial and chemical changes that follow experimental feeding of cholesterol and excess of fat to chickens at varying ages.[103,104] The lesions produced in this manner differ in many respects from those developing spontaneously or following the use of estrogen. From the beginning they resemble human atheroma and include the formation of foam-cell plaques, necrosis, fibrosis, hyalinization, calcification, and cartilaginous and osseous metaplasia. Ulceration of the atherosclerotic plaques with thrombus formation is the only lesion of man which has not been noted in the chick. Lesions may form in the entire length of the aorta and in the coronary arteries. Accompanying these anatomic changes there is a great increase in the concentration of cholesterol, a disproportionately small rise in the phospholipids, and consequently an elevated cholesterol-phospholipid ratio.

E. *The Effects of Administration of Estrogen in Cholesterol-Induced Atherosclerosis.*—Pick, Stamler, Robbard, and Katz[103] were responsible for the extraordinarily significant observation that estrogen combined with cholesterol feeding inhibits prophylactically the development of coronary atherosclerosis, but has no perceptible effect on the formation of lesions in the aorta. It also permits a rise in phospholipids more commensurate with the increase in cholesterol that follows cholesterol feeding. The cholesterol-phospholipid ratios of plasma are much less elevated than when the cholesterol feeding is conducted alone. It was found that there is a close correlation between the level of the cholesterol-phospholipid ratios and the degree of atherogenesis. Thus all estrogen-treated birds that failed to develop coronary lesions had cholesterol-phospholipid ratios below 0.80.

It was shown further[104,105] that the estrogens may exert a therapeutic effect. In chicks that were fed for several weeks on a cholesterol-supplemented diet adequate to induce extensive coronary lesions, estrogen administration for a few weeks caused regression of the coronary atherosclerosis.

It was also shown by Katz and his co-workers[104] that the cholesterol-induced coronary atherogenesis which is prominent in cholesterol-fed roosters does not appear in the egg-producing hen. Thus sexually mature male and female chicks exhibit, like human beings, a significant sex difference in their susceptibility to coronary atherosclerosis.

These experiments appear to afford a clean-cut demonstration that atherogenesis proceeds according to different laws in different vascular beds.

Katz[104] has also shown that androgens given simultaneously with estrogens tend to prevent the feminizing effects of the estrogen but do not interfere with the inhibitory action of estrogen on cholesterol-induced coronary atherogenesis.

III. EFFECT OF ADMINISTERING GONADAL HORMONES IN MAN

A. *Effect of Estrogens.*—The possibility that women before the menopause are protected by estrogenic hormones has received some support from the recent report of Wuest, Dry, and Edwards,[106] who observed that the incidence and severity of coronary atherosclerosis following bilateral oophorectomy approaches that of the male.

The effect of estrogens has been tested. Eilert[107,108] reported that the oral administration to menopausal women of daily doses of 0.05 to 0.10 mg. of ethinyl estradiol resulted in an average decrease in the serum cholesterol level together with an average increase in the serum phospholipid content. Barr, Russ, and Eder[109,110] reported that in survivors of myocardial infarction, an oral dose of 1.0 mg. per day of ethinyl estradiol or an equivalent amount of Premarin was followed by a diminution in the level of serum cholesterol and an increase in the concentration of phospholipids. The direction and rate of the change following the use of the estrogen are indicated in Table XII.

TABLE XII. EFFECT OF ADMINISTRATION AND WITHDRAWAL OF ESTROGEN IN 20 SURVIVORS OF MYOCARDIAL INFARCTION (BARR[35])

STAGE OF TREATMENT	TOTAL CHOLESTEROL (MG. PER 100 ML.)	CHOLESTEROL IN ALPHA LIPOPROTEINS		CHOLESTEROL IN BETA LIPOPROTEINS (MG. PER 100 ML.)
		PER CENT OF TOTAL	MG. PER 100 ML.	
Before estrogen	282	11.3	32	250
After 1 week	283	16.7	41	243
2 weeks	270	17.5	47	223
3 weeks	260	19.0	49	211
4 weeks	251	21.0	53	198
5 weeks	247	22.0	55	191
6 weeks	225	25.4	57	168
7 weeks	222	25.0	56	166
8 weeks	216	26.0	56	160
9 weeks	210	27.1	57	153
Two weeks after discontinuing estrogen	285	18.5	53	220

Changes were also noted in the cholesterol-phospholipid ratio of the plasma, which dropped from a mean value of 1.05 to 0.72.

Marett and Vivas[111] showed reduction in total lipids and total cholesterol following small daily doses of Premarin over a period of twenty-five weeks. His subjects included 12 men who had survived myocardial infarction, 5 others with miscellaneous conditions, and 1 woman who had survived a cerebral vascular accident. Gertler, Hudson, and Jost[112] found some increase in serum phospholipid level without change in the concentration of serum cholesterol in 25 patients who received daily doses of 500 mg. of stilbestrol following bilateral

orchidectomy for carcinoma of the prostate. Similar effects of estrogen have been reported also by Oliver and Boyd,[113] who showed that ethinyl estradiol in doses of 0.4 mg. each day depressed the plasma ester cholesterol in 20 hypercholesterolemic men with coronary disease without influencing the serum level.

Somewhat difficult to correlate with other reports is the observation of Ahrens, Payne, Kunkel, Eisenmenger, and Blondheim[114] that the administration of estrogen in patients with biliary cirrhosis causes visible lipemia of the serum with an increase of both neutral fats and phospholipids.

The only completely discordant result concerning the action of estrogens is in the reports of Engelberg, Glass, and Marcus[115] and Glass, Engelberg, Marcus, Jones, and Gofman,[116] who in a study of 16 men and 15 women in the age group from 55 to 65 found no evidence that estradiol in doses of 0.25 mg. daily for periods of two to four months influenced the level either of the serum lipids or of the low-density proteins.

B. *Effect of Androgens.*—The effect of androgens on the protein-lipid relationships of plasma appears to be precisely opposite to that of estrogen.[85] With the use of oral methyl testosterone in a miscellaneous group of cases including normal individuals and survivors of myocardial infarction, Russ, Eder, and Barr[117] found a relative decrease in the cholesterol combined with alpha lipoprotein and a corresponding decrease in the amount combined with beta lipoprotein. In some of the patients the concentration of cholesterol in the unfractionated plasma was augmented and the cholesterol-phospholipid ratios increased. Abnormality in distribution of lipids found in survivors of myocardial infarction was increased, and previously normal lipid patterns were changed to simulate those of survivors of infarction. The direction of the change in the distribution of cholesterol is indicated in Table XIII.

TABLE XIII. EFFECT OF ADMINISTRATION AND WITHDRAWAL OF METHYL TESTOSTERONE (RUSS, EDER, AND BARR[117])

SUBJECT	PER CENT OF TOTAL CHOLESTEROL IN ALPHA LIPOPROTEINS		
	BEFORE TESTOSTERONE	AFTER TESTOSTERONE	AFTER WITHDRAWAL OF TESTOSTERONE
Po	8.8	5.2	11.1
Ia	16.0	11.1	21.4
Ma	18.0	10.7	16.7
Cr	18.1	8.7	17.3
Ra	18.9	13.6	23.8
Cu	21.5	12.1	23.3
Wa	26.1	15.9	22.0
Bi	27.1	16.1	26.7
Gu	27.6	13.3	20.4
La	27.9	21.6	24.3
Ba	28.4	18.3	28.4
Ru	35.4	26.4	30.0
Average	22.8	14.4	22.1

C. *Effect of Simultaneous Administration of Estrogens and Androgens.*—Observations were made by Russ, Eder, and Barr[117] on the simultaneous administration of estinyl and methyl testosterone. The results in a typical trial are presented in Table XIV.

TABLE XIV. EFFECT OF SIMULTANEOUS ADMINISTRATION OF ESTINYL AND METHYL TESTOSTERONE IN A SURVIVOR OF MYOCARDIAL INFARCTION (RUSS, EDER, AND BARR[117])

DATE	STATE	CHOLESTEROL (MG./100 ML.)	CHOLESTEROL IN FRACTION IV + V + VI ALPHA LIPOPROTEINS (PER CENT OF TOTAL)
1/17	No treatment	202	9.7
	Estinyl 1.0 mg. q.d. started		
5/22	Estinyl dosage reduced to 0.5 mg. q.d.	173	29.6
8/1	Estinyl dosage reduced to 0.25 mg. q.d.	194	33.1
9/25	M.T.* 50 mg. q.d. started	217	31.2
10/23	M.T. discontinued	351	3.2
12/11	M.T. 10 mg. q.d. started	226	27.6
2/5	Estinyl dosage increased to 1.0 mg. q.d.	274	8.0
3/12	Estinyl dosage reduced to 0.5 mg. q.d.	261	8.3
4/9	M.T. dosage reduced to 5.0 mg. q.d.	248	8.0
5/14	All hormones discontinued	221	14.5

*Methyl testosterone.

In the doses given, the action of methyl testosterone on the distribution of lipids in plasma was far more potent than that of estinyl. The action of the androgen obliterated completely the chemical effects of the estrogen, a result that did not seem to conform to experience with combined estrogen and androgen therapy in the chick.[104]

These observations on the combined action of the two hormones as well as those on the effect of an androgen when given alone raise the question as to whether differences in atherogenic tendency between males and females are due to the protective influence of estrogen or to the deleterious action of androgen.

SUMMARY

Although the extent of lipid deposit in most arteries differs little in men and women, there is some precocity of its development in the coronary arteries of men. Angina pectoris, coronary occlusion, and myocardial infarction rarely occur in women before the age of 40. Arteriosclerotic disease of the vessels of the legs is more common in men. The suceptibility of men and the relative immunity of young women to serious consequences of coronary and peripheral atherosclerosis are not satisfactorily explained by anatomic differences in the sexes. The relative incidence of severe or fatal complications cannot be explained by any demonstrable variation with sex in the concentration of total lipids, cholesterol, or phospholipids. Sex-linked differences in the distribution of lipoproteins can, however, be demonstrated by Cohn fractionation of plasma or by the methods of paper electrophoresis and ultracentrifugation. Young men tend

to have in their plasma a greater concentration of beta lipoproteins, a smaller amount of alpha lipoproteins, a higher beta-alpha ratio, and a larger content of S_f 10—20 lipoproteins. Action of heparin in clearing alimentary hyperlipemia is less prompt in young men. The number of mast cells in their tissues is less than in young women. None of these distinguishing features of sex are apparent in the aged. Both the incidence of clinical complications and the distinctive differences in the state of lipids in the plasma are less prominent after the time of the menopause. That the chemical differences between young men and women have some relationship to the development of atherosclerosis is indicated by the demonstration that states of relative freedom from the disease are accompanied by lipid patterns like those of young women, and that diseases and conditions which are accompanied by advanced atherosclerosis or are known to be atherogenic have patterns that are exaggerations of those found in young men.

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Studies of conditions in the domestic fowl have shed some light on the nature of sex-linked differences in the development of atherosclerosis. Spontaneously occurring arterial lesions in the rooster and in the mature egg-laying hen are quite different, although it is doubtful whether either is comparable to human atheroma. Puberty in the hen and the administration of estrogens to the immature or male chick are accompanied by hyperlipemia which in its degree is without counterpart in human physiology. Such gross species' differences have made difficult the application of knowledge derived from the study of the fowl to the problems of human atherosclerosis. It has been shown in the chick, however, that experimental cholesterol-induced atherosclerosis causes extensive atheromatous lesions of the aorta in both the hen and the rooster. It causes coronary atherosclerosis in the male bird but not in the laying hen. It has been shown also that the administration of estrogen inhibits prophylactically the development of coronary atheroma but does not affect lipid deposit in the aorta. Estrogen also has a therapeutic effect in causing regression of coronary atheroma without modifying the degree of aortic atherosclerosis. These anatomic effects of estrogen are accompanied by modification of the chemical changes consequent to cholesterol feeding, and particularly are responsible for an increase in the concentration of phospholipids and a lowering of cholesterol-phospholipid ratios. They are not reversed in the chick by simultaneous administration of androgen.

In man the administration of gonadal hormones is accompanied by profound changes in the distribution of lipids in the plasma. Estrogen transforms the highly abnormal lipid pattern of myocardial infarction to one that is indistinguishable from that of healthy young women. Methyl testosterone exerts an opposite action: it exaggerates the lipid abnormality of survivors of myocardial infarction; it produces patterns similar to those of coronary atherosclerosis in individuals whose plasma has previously shown no lipid abnormalities. Contrary to the experience in the chick, the administration of androgens simultaneously with that of estrogens obliterates the chemical effects of the estrogens.

The accumulated clinical and experimental evidence leaves little doubt that sex is a potent factor in the development of atherosclerosis, and that its influence is hormonal and is accompanied by easily recognizable changes in the distribution of lipids in plasma. There is much reason to believe that the development of

coronary atherosclerosis and its complications is dependent upon factors not equally operative in other arterial systems.

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Editorials

THE CHANGING ROLE OF CHRONIC DISEASE

Man's experience with illness in this country has been rapidly changing from those processes classified as acute to those classified as chronic. When acute disease was rampant, attention was heavily focused on sheer survival, and the general measure of health that was considered appropriate was the mortality rate.

As chronic illness has come to the fore, there has been a change of emphasis. The question as to whether a person with a chronic condition dies or when he dies is beginning to take second place to a consideration of the degree of his disability as he lives with the disease and of such social measures as care and rehabilitation that are involved in the adjustment of the patient to society.

The rapidity with which this change has come about, together with the need for new yardsticks for measuring the effects of chronic disease, has made it difficult, even for students devoting themselves particularly to this problem, to get a real measure of the course of events.

We do know that, while chronic disease strikes less frequently than acute, it causes the major portion of the disability from which people suffer. In the ages over 10, more than 60 per cent of the disabled days are due to chronic disease, and this proportion rises with increasing age. We must not, however, make the mistake of thinking that the chronic disease problem is mainly one of the aged, for, in fact, three-fourths of the invalids suffering from chronic illness fall in the ages under 65.

At any one time, approximately 4,000,000 of our people are suffering from serious chronic illness or disabling conditions.

Not only do these figures indicate a serious current situation, but the continued decline in acute conditions and the increase in the average duration of life in our population mean that it is becoming more and more serious.

The sheer problem of care of the number of people involved is a massive one. We must have facilities for home care, nursing and convalescent homes, hospitalization provision, and we require available diagnostic clinics and rehabilitation centers. A variety of professional and semiprofessional skills are involved. We are short on these provisions and, furthermore, have little or no coordination of the services that are available. Experiments in such coordination are needed. These should lead to some system so that a chronic disease patient will not be trapped in his own home or in a home-care institution and fail to receive the diagnosis and treatment that might alleviate his condition or the rehabilitation services that might restore him to a useful place in society.

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The great need, however, is for more fundamental knowledge with regard to the conditions themselves. This calls not only for a research program devoted to chronic disease, but it means much more intensive research on the whole subject of the biologic changes involved in the aging process. The very fact that chronic conditions extend over a long period of a person's life makes it difficult and at times impossible to interpret the specific findings of chronic disease studies without knowledge of the normal biologic changes that are going on. The total research problem is therefore complex and one that will need to be approached from many different directions.

It is timely that we have a journal for bringing together the research in this field.

LOWELL J. REED

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CHRONIC ILLNESS AND THE MEDICINE OF TOMORROW

This publication of the first issue of the JOURNAL OF CHRONIC DISEASES in itself illustrates that the primary problems of medicine have changed, particularly in the past decade. These changes have come about as a result of new surgical techniques, the conquering of many of the infectious diseases, the new era of physiologic understanding made possible by the steroid hormones, and scores of other advances in medical research. Now, of necessity, medicine must change from a primary emphasis on the immediate manifestations of acute diseases to an all-out frontal attack on their later sequelae and on the problems of chronic illness.

This is more difficult than it sounds.

Our national military establisment has termed its program of appraisal, evaluation, and integration of newly developed atomic weapons, guided missiles, and speedier planes into existing concepts of military strategy and tactics as the "new look." Similarly, we in medicine must appraise, evaluate, and integrate new weapons in our armamentarium and alter our existing concepts of medical tactics and strategy in meeting the changed problems presented by our patients.

In the past the dramatic in medicine has been the difficult diagnosis, high fever, acute illness, the life and death decision. The scores of great books, plays, and motion pictures involving medicine have reached their climaxes around these dramatic factors.

If, however, we are to meet the problems of chronically ill people, if we are to save not only their lives but their dignity and purpose, if we are to preserve their residual abilities and make it possible for them to be useful citizens, the focus of the drama of medicine must be changed.

Starting with undergraduate teaching, the medical student must be indoctrinated by example as well as precept to the glamour and warm inner satisfaction that comes from aiding the chronically ill individual to meet his total life needs. He must learn to get an ego glow from taking the old hemiplegic out of a wet bed, teaching him to walk and to talk, to meet the needs of daily living and to live outside an institution, and to be a person again. These accomplishments must give him the same satisfaction that he now gets from making a diagnosis of favism or anthrax.

If he does not develop such a feeling of inward satisfaction, much of his professional life will be frustration. Whether he likes it or not, the average general practitioner now spends three-quarters of his time treating patients who are chronically ill or who have emotional problems involving social, marital, or economic pressures. This percentage will undoubtedly increase continually in the future.

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When the medical student or young physician reaches the point of feeling a deep sense of accomplishment from his efforts to aid the chronically ill and disabled, then he ceases to be a technician and becomes a physician in the true sense of the word, for then he treats people rather than diseases.

As a result of the dramatic advances in definitive medicine and surgery, each year hundreds of thousands of persons leave our hospitals alive who, with the same illness or injury five years ago, would have died. However, many of them who leave the hospital "cured" also leave with a serious residual chronic disease and disability. Each of them represents a precious human life saved, yet each raises the question of whether the same society which can save a life can also give meaning to it. Providing that meaning is the drama of the medicine of tomorrow.

HOWARD RUSK

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SOME OBSERVATIONS ON THE BEGINNINGS OF CHRONIC DISEASE

When the opinions of leaders in the profession were sought regarding the advisability of launching this JOURNAL, four respondents, favorable to the idea, offered the interesting suggestion that the content of the publication might profitably be devoted to the beginnings of chronic disease. This approach, while orthodox for the illnesses initiated by microbic agents, has only recently come to influence the orientation of research in such prolonged diseases as, for example, chronic glomerular nephritis, primary (essential) hypertension, arteriosclerosis, the cirrhoses of the liver, and the degenerative joint disorders. It is sometimes assumed that the so-called "degenerative diseases of middle life" are initiated about the age of 40. Recent additions to our knowledge indicate that this concept requires reappraisal.

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The physician's experience points out that cardiac failure in middle life may be related to rheumatic fever or syphilis contracted in youth. In these examples of the deferred sequelae of microbic infection, the relation of the beginnings of a pathologic process to a distant chronic state is evident. The pathogenesis of some other long-term illnesses is less clear if the etiological agent is unknown, as in rheumatoid arthritis or primary hypertension. An inquiry will now be made into the clinical and pathologic evidence for early, specific, usually symptomless abnormalities in a limited number of chronic diseases in which organ failure occurs years or decades after the onset of the disease.

Until Bennett, Waine, and Bauer's report[1] in 1942 on the "Changes in the Knee Joint at Various Ages," it had been generally assumed that osteoarthritis or hypertrophic arthritis represented a classical example of a degenerative disease limited to later life. Their data represented a comprehensive and precise study of knee joints obtained post mortem or by amputation from sixty-three patients whose age ranged from 1 month to 90 years. The hospital records for each of these individuals gave no evidence that the knee joints had ever been the source of symptoms or abnormal physical signs. Nevertheless, the pathologic examination revealed that some degeneration of the knee joint was present in every subject over 15. Bennett and his colleagues found that the process "first becomes manifest in the superficial layer of articular cartilage of individuals in the second and third decenniums. This tissue, smooth, glistening, translucent, resilient, and bluish-white in normal growing subjects, acquires a yellowish, more opaque coloring and, while firmer, a progressive loss of elasticity. Concurrently, the surface layers exhibit small blisters, linear grooves, and pits in those areas in which weight-bearing is pre-eminently concentrated and which are most severely subjected to shearing and twisting types of stress (patella, exposed portions of the tibial condyles, and patellar surface of the femur)." Bennett, Waine, and Bauer considered the disease primarily a degenerative process of hyaline cartilage and

concluded that the specimens which they had collected from individuals without joint symptoms indicated that "all those past the second decade of life showed, progressively, evidence of this disorder." Other investigators[2] had previously demonstrated similar early lesions in post-mortem human material, in cattle, and in horses. It would thus appear that, at least with respect to the knee joint, this common arthropathy, usually considered a "degenerative disease of middle or late life," has its beginnings by the end of the second decennium.

Primary (essential) hypertension has long been known to be a major cause of death in middle life. Exacting clinical studies and data accumulated from college hygiene departments indicate that the appearance of an abnormally elevated blood pressure may be detected in early adult life. Furthermore, Chasis,[3] in a textbook of pediatrics, stated that "a few well documented cases of advanced hypertensive disease in the first decade of life are recorded . . . it may be that the disease has its onset early in life more frequently than is realized." Hines[4] reported in 1937 that 18 per cent of 400 children between the ages of 6 and 19 years exhibited a hyperreaction in both systolic and diastolic blood pressure to a standard stimulus (cold pressor test). He felt that this response was indicative of a prehypertensive state. This hypothesis received support from a subsequent follow-up study reported by Hines[5] in 1950 in which it was shown that "of 206 patients who had recently had essential hypertension, 86 per cent had, from 10 to 20 years previously, given evidence of a hyperreaction of this probably neurogenic mechanism (cold pressure test) for regulating the blood pressure, although they had a usually normal blood pressure at that time and did not present the clinical picture of essential hypertension until a number of years had elapsed."

Diehl and Hesdarffer[6] reported a follow-up study of 155 students at the University of Minnesota in which it was apparent that those individuals who, at the average age of 19.8 years, showed abnormal elevations of blood pressure, even if transitory, were more likely to have high blood pressure at the average age of 26.8 years than men whose blood pressure at the earlier average age was consistently within the so-called normal limits. G. A. Perera[7] (whose contribution on the natural history of hypertensive vascular disease appears in this issue) has indicated his conviction that the first manifestations of hypertensive vascular disease begin in youth and early adult life in the majority of instances. Perera[8] reviewed the life history of 100 patients with hypertensive vascular disease. The survey was limited to those patients in whom the time of onset could be established by the following criteria: "the first appearance of an abnormal elevation of blood pressure (repeated casual diastolic readings of 90 mm. Hg or more) and . . . a known period of normotension recorded not longer than two years before." In this selected group the average age of onset of the disease was found to be 32 years and the average age at death 52 years.

In a provocative physiologic and genetic study involving 875 subjects, Hines[9] found that "when both parents had a normal blood pressure and were normal reactors (to the cold pressor test), all the children were normal reactors. If both parents had hypertension or were hyperreacting normals, 95 per cent of the children had hypertension or were hyperreactors to the test, and if one

parent had hypertension or was a hyperreactor and the other parent was a normal reactor, 43.4 per cent of the children were hyperreactors or had hypertension. In three families of two generations, the parents had essential hypertension or had died of it and all of the children had hypertension or were hyperreactors." Ayman[10] presented data leading him to conclude that the "so-called emotional hypertension" of young adults was almost wholly limited to children of hypertensive parents.

An appraisal of these data indicates that genetic factors appear to play an important role in the initiation of primary hypertension; that under appropriate conditions the disease may be detected in youth; and that in the majority of instances primary hypertension, if it is to occur, develops in early adult life.

Atherosclerosis is often referred to as a prime example of a "degenerative disease of middle life." Increasing knowledge indicates that this disease may be associated with a derangement in lipid or lipoprotein metabolism.[11,12] Local anatomic factors usually determine the nature of the arterial lesion and the resultant clinical state. It is noteworthy, nevertheless, that many individuals can live to old age despite the presence of advanced lesions. Atherosclerosis is not a necessary concomitant of ageing. Groddeck[13] reported that the post-mortem examination of 283 individuals over the age of 80 revealed no striking evidence of the disease in 3 per cent of the subjects. It was further found that although the coronary arteries were the most frequent site of the disorder, these vessels exhibited only minimal lipomatosis in 34 per cent of this aged group.

It has long been appreciated that unequivocal evidence of intimal atherosclerosis is present in the majority of individuals after the age of 30. Recently interest has been renewed in the concept that the beginnings of the disease probably occur earlier in life. This information comes from several areas of investigation. In an analysis of juvenile atherosclerosis, Griffin, Strong, and Holman[14] compared the aortas of 102 consecutive hospital subjects in the age group 1 to 17 years with those from a smaller group of similar age obtained from the coroner's office. They found that the terminal illness did not influence the presence or absence of aortic lesions, since the aortas of the individuals who had come to sudden or violent death were indistinguishable from those of the hospital patients. Every aorta from the subjects beyond the age of 3 years "had one or more focal deposits of material which was visible on the intimal surface after staining with Sudan IV. No typical pearly placques were found in this age group." Since this lipid deposition was found in each aorta from subjects 4 to 17 years of age, it is reasonable to believe that spontaneous reversibility of this process is uncommon, but this point remains to be proved. The failure to observe the characteristic pearly placque of atherosclerosis may be related to the age and intensity of the lesion since this feature is seen commonly after 30.

Atherosclerosis may be found in the aortas of children in whom a disordered lipid metabolism has been part of the clinical picture of the nephrotic syndrome or of severe diabetes mellitus. An understanding of the mechanism of another childhood pathologic state might throw further light on the nature of atherosclerosis. This disease, progeria, which first becomes manifest at approximately 1 year of age in a previously healthy infant, is characterized by dwarfism,

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by a loss of hair and subcutaneous fat, and by the *precocious development of atherosclerosis*. Among the few case reports available concerning this syndrome is that by Talbot and associates.[15] The clinical picture in this instance was typical, and the last year of the boy's life (from age 6½ to 7½) was characterized by a symptom complex pointing to coronary artery insufficiency. Post-mortem examination revealed severe generalized arteriosclerosis, severe coronary artery sclerosis with probable occlusions, and recent and old cardiac infarctions.

It is thus seen that although the lethal effects of atherosclerosis are chiefly apparent in middle and late life, the disease is unequivocably evident in the majority of individuals in the United States after the age of 30, and probably exists in larval form after the fourth year of life. During childhood, in the special instances of the nephrotic syndrome, diabetes mellitus, and progeria, atherosclerosis may be present in a state comparable to that observed in middle or late life. An appraisal of these facts lends weight to the concept that the beginnings of atherosclerosis occur in childhood and in a sense points up a pediatric aspect of geriatrics.

Mental disorders account for much disability in the middle and late decenniums. In so far as syphilis and atherosclerosis play a causative role in the organic psychoses, there is no doubt that the onset of these underlying diseases long precedes the disturbances in the affect. Kallmann[16] has presented evidence indicating that polygenetic factors may in part contribute to the development of a senile psychosis. He has found that "the expectancy of this type of psychosis is significantly increased in senile twin sibships varying from 6.5-8.0 per cent for sibs and two-egg cotwins to 42.8 per cent for one-egg twins." This five- to sixfold increase in frequency emphasizes the genetic influence in this disorder. Zeman's[17] experience has led him to the belief that the mental abnormalities observed in the aged are not necessarily due to advanced years but can often be related to personal maladjustments of long duration. Zeman stated that "immature, compulsive, narcissistic and psychopathic personalities often attain old age without the improvement or 'mellowing' that long years are popularly supposed to bring." The physician frequently sees patients who appear to be experiencing their first symptoms of mental disorder in middle or late life. Psychiatric investigation would seem to indicate, however, that this observation is more apparent than real. Both Kraepelin and Reiss[18] were impressed by the prepsychotic manifestations of the manic-depressive psychoses. They observed this predisposition for a manic, depressive, irritable, and cyclothymic make-up in 60 to 80 per cent of their patients. In this connection, H. D. Palmer[19] has added information concerning the early background of involutional psychosis by stating that "there are unique personality trends visible throughout the life history of the individual who ultimately develops involutional melancholia."

The stigmas of some other chronic illnesses are detectable early in life. This is particularly noted in a number of biologic defects in which the genetic factors are clearly defined. Included in this group are such relatively uncommon diseases as hemophilia, sickle-cell anemia, cystinuria, phenylpyruvic oligophrenia, and progressive muscular dystrophy. More common chronic disorders of middle or late life, such as gout, diabetes mellitus, and chronic cholecystitis, are coming

to be recognized early in life because of increased clinical awareness and improved diagnostic measures. Griffin and Smith[20] surveyed the records of 245 permanent residents of Rochester, Minnesota, in whom the diagnosis of gall bladder disease was established at the Mayo Clinic during the years 1948 and 1949. They concluded that "the dictum 'fair, fat female of 40' as a concept of the typical patient who has disease of the gall bladder be abandoned because it can lead to serious error." Despite the limitations of the study, which Griffin and Smith pointed out, it was shown that cholecystic disease occurred in all age groups from 15 to 76 or more and that there were as many patients with the disorder between the ages of 26 and 30 as between the ages of 41 and 45. In fact 3.3 per cent of the patients were 20 years or less, 2.9 per cent were between 21 and 25 years of age, and 8.2 per cent were between the ages of 26 and 30. The authors emphasized the frequent occurrence of cholecystitis in adolescents and young adults and pointed out that failure to appreciate this fact led to a number of erroneous initial diagnoses in their series.

The data presented here support the concept that many chronic diseases have their beginnings before organ insufficiency is apparent. Such an orientation suggests increased opportunities for early diagnosis and testing of various agents offered for the prevention and management of chronic diseases. The control of early syphilis forestalls the occurrence of a segment of cardiovascular disease and dementia; the control of group A hemolytic streptococcal infections reduces the frequency of crippling attacks of rheumatic heart disease; adequate diets effect a more favorable outlook for the patient with early Laennec's cirrhosis; and vitamin B_{12} maintains the patient with pernicious anemia. These are but a few examples of beneficial approaches to chronic diseases in their early phases. In the field of mental hygiene and preventive psychiatry, the belief is held that each personality reflects the impact of life situations upon a genetically governed human being. Since both these forces are in effect at birth, it follows that opportunities become available to the family physician or psychiatrist early in the patient's life favorably to modify reactive tendencies which may be disadvantageous to the individual.

In the past it was chiefly the endings of chronic disease which attracted the attention and care of the physician. Today the beginnings of long-term illness are becoming apparent to the doctor because of painstaking clinical, physiologic, biochemical, and pathologic studies. This new knowledge must perforce accelerate the rate of development of therapeutic measures.

DAVID SEEGAL

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LUNG CANCER

In the early years of the twentieth century the diagnosis of lung cancer was a rare event. In fact, deaths were so infrequently attributed to cancer of the entire respiratory system that it was not identified separately in United States mortality statistics until as late as 1914. The rapid rise in lung cancer mortality during the past two decades has now become a matter of grave concern to the medical profession and the public. In 1930, less than 3,000 of almost 1,500,000 deaths in the United States were ascribed to lung cancer; preliminary statistics for 1953 indicate that of the same total number of deaths, about 22,000 were attributed to this disease. It has now become the leading site for cancer mortality among males. The explosive nature of the change in mortality is most unusual for a so-called chronic disease; such a pattern has never been observed for cancer of other sites.

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This phenomenon has not been confined to the United States. On reviewing the evidence, Dorn[1] concluded, "Today one can fairly say that cancer of the lung exists as a pandemic disease in North America and in the industrialized countries of Northwest Europe." A Danish investigator, Clemmesen,[2] described the increase in the absolute incidence of lung cancer as "the most violent phenomenon in the history of cancer." The United States is not even in the front rank of countries with high mortality rates. Dunn,[3] in examining the data for fourteen countries with well-developed vital statistics systems, found that the United States ranked seventh in lung cancer mortality. The dubious distinction of first place must be accorded to England and Wales. The evidence for an increase rests principally on, but is not confined to, data supplied by vital statistics offices. Doll[4] has reviewed several necropsy studies which support this finding. Hueper,[5] dealing with similar evidence, claimed that the increase started long prior to its reflection in mortality statistics.

Only one-twentieth of the recorded increase in lung cancer mortality in the United States between 1930 and 1950 can be assigned to the aging of the population, associated in part with the reduction in mortality from other causes. Another portion of the increase is due unquestionably to improvements in diagnosis. However, the consensus among leading investigators, in the words of the Louvain Symposium on the Endemiology of Cancer of the Lung,[6] is that "a significant part of this increase is absolute and represents a real increase in the number of people suffering from primary cancer of the lung." A few dissenters[7] remain, who hold that the recorded increase is purely fictitious. The observations incompatible with the sole explanation of improvement in diagnosis have recently been summarized by Dunn[3]:

(1) The disproportionate gap in mortality between the two sexes, the increase in the rates for males far outstripping those for females;

(2) the variation in rates of increase when examined by age groups;

(3) the magnitude of the current, continuing increase, admittedly without commensurate improvement in diagnostic facilities and techniques.

There is every reason to believe that, although there has been some slackening of the rate of increase, lung cancer mortality will continue to increase in the foreseeable future. When the experience of cohorts (persons born in the same year or group of years) born around 1870, 1880, 1890, and so forth, is traced, it is found that lung cancer mortality begins to play a significant role around age 40 and increases in magnitude thereafter. Furthermore, each succeeding (younger) cohort has experienced increased mortality from this cause. Conservative projections of present trends suggest, for example, that by 1980 the death rate per 100,000 for white males 65 to 74 years will be 215 contrasted to the figure of 105 observed for 1950. On the basis of rates projected in this manner, the "betting odds" are about 4.3 in 100 that a white male between 30 and 50 years of age will develop lung cancer sometime during his life.[8]

Of the several general factors known to govern cancer risk, it is difficult to believe that changes in the genetic composition of the population could have occurred in sufficient magnitude to account for the increase. This leaves a variety of environmental factors as possible causes of the phenomenon. Since abundant animal and human evidence suggests a long latent period between exposure to a carcinogen and disease development, attention has been directed to environmental changes which occurred 15 to 25 years prior to the increase.

The possible environmental changes, not mutually exclusive, which have been suggested as causal factors, fall into three major categories:

(1) Increase in use of tobacco;

(2) increased atmospheric pollution by the effluents of an industrial civilization, such as motor vehicle exhausts, products of tarred roads, factory wastes, and so forth;

(3) increase in special occupational hazards involving industrial exposure in producing or processing chromate ores, illuminating gas, radioactive ores, and a variety of other substances.

The existence of special occupational hazards cannot be doubted. However, the employee groups are numerically insignificant and this class of risks cannot possibly account for any but a very small part of the observed increase. The atmospheric pollution theory relies mainly on urban-rural differentials in mortality, plus the demonstration in urban atmosphere of substances which are carcinogenic to animals. Such agents were extracted from the atmosphere as early as 1942,[9] and recently Kotin[10] has identified 3,4 benzpyrene, a proved laboratory animal carcinogen, in motor vehicle exhaust gases. Inability to classify the population by degree of exposure to atmospheric pollution and to compute attack rates for groups of people with varying exposure has been a major deterrent in testing the hypothesis of atmospheric pollution as a cause of this disease.

The evidence linking tobacco smoking to lung cancer is much more convincing.[11] At least thirteen retrospective studies conducted during the past fifteen years in five different countries, comparing smoking history in diagnosed lung cancer cases with that from a variety of controls, have uniformly concluded that the risk of lung cancer among smokers exceeds that among nonsmokers. Relative risks for smokers compared to nonsmokers have ranged from about two to fourteen times in the different investigations. These studies incriminate cigarette smoking to a stronger degree than cigar or pipe smoking.

Cutler and Loveland[8] have summarized the results of three sets of these recent investigations in terms of cases of lung cancer expected to develop before age 80 among 1,000 white men now 40 years of age: nonsmokers, 6; one-half pack or less daily, 25; one-half pack to one pack, 49; more than one pack, 80.

Preliminary results from a forward-looking study among smokers and nonsmokers recently reported by Hammond and Horn[12] lend support to these estimates. The findings of the latter authors lead them to assert cause-effect relationship between cigarette smoking and lung cancer. They obviously cannot claim it as the sole cause, however, since the disease occurs, although less frequently, in nonsmokers. Even prior to this study few workers had seriously questioned the statistical association between lung cancer and smoking, particularly cigarette smoking, or that the association is in general proportional to total tobacco consumption.[13] Controversy revolves around whether this association represents a cause-effect relationship or whether smoking is associated in some undetermined way with other unidentified factors. The issue of association with other factors cannot be resolved in the form of a clinical trial in which exposure to tobacco smoke is assigned in advance, since smoking histories must be accepted as found in the population. The conclusions of the Standing Advisory Committee on Cancer and Radiotherapy to the British Minister of Health summarize one body of prevailing opinion.

"(1) It must be regarded as established that there is a relationship between smoking and cancer of the lung.

"(2) Though there is a strong presumption that the relationship is causal, there is evidence that the relationship is not a simple one, since:

"(a) the evidence in support of presence in tobacco smoke of a carcinogenic agent causing cancer of the lung is not yet certain;

"(b) the statistical evidence indicates that it is unlikely that the increase in the incidence of cancer of the lung is due entirely to increases in smoking;

"(c) the difference in incidence between urban and rural areas and between different towns, suggests that other factors may be operating, e.g., atmospheric pollution, occupational risks."

This position could be modified by new evidence. For example, the American Cancer Society and the National Cancer Institute (in cooperation with the Veterans Administration) are each conducting a forward-looking study of mortality among male smokers and nonsmokers. Here smokers and nonsmokers

can be classified with respect to place of residence, occupational history, and possibly other variables. If it is found that the relationship between cigarette smoking and lung cancer holds consistently within a variety of subgroups, the case for cause-effect relationship will be greatly strengthened.

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ON MUSCULAR CRAMPS

Man is heir to a multitude of uncomfortable minor maladies, often persistent or recurrent. Happily, the greater number of these constitute no threat to life; nevertheless, many of them are annoying and may effect some handicap. On infrequent occasions, some of these minor disorders are ominous harbingers of disastrous disease, and their appearance thus may become the basis for an anxiety which in most instances is needless. Muscular cramp is one of these common occurrences, and virtually every person has experienced it one or more times.

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Normally, graded muscular contraction results from the repeated operation of varying numbers of motor units, each of which is a leash of muscle cells all innervated by branches of a single axon arising from one motor anterior horn cell. The force exerted by a contracting muscle is proportional to the number of motor units which are contracting and the frequency at which they repeat their unitary activity. Under normal circumstances the repeating frequency in a motor unit is somewhere between 10 and 50 per second, depending on the type of muscle and the work it is called on to perform. When contraction is sustained, the motor units alternate, so that at any one instant only a fraction of the available fibers is contracting while their neighbors are quiescent. It is impossible virtually to effect simultaneous contraction of all fibers in a muscle by voluntary means. The limit thus set would seem to account for the fact that maximum *voluntary* contraction does not produce pain in the muscle itself. In myotonia, the rate of discharge of a single muscle fiber may range up to 100 to 150 per second, but the contractions of the muscle fibers are asynchronous so that the total force does not exceed that developed during voluntary contraction; and this sort of abnormal muscle activity also does not evoke pain. Cramps, on the contrary, are marked by pain in the muscle and have been shown to result from continuous firing at very high frequencies (up to 300 per second) of most if not all of the motor units in the muscle in spasm. It would appear likely that the characteristic pain is associated with the excessive contraction induced by the wildly repetitive firing of the motor units. The luxuriant sensory innervation of muscle (spindles) is adapted almost entirely for the centripetal relay of information concerning stretch; the appreciation of excessive tension as pain is not understood but is comparable perhaps to similar phenomena occurring so familiarly in distended smooth-muscled viscera like gut and bladder.

Most muscular cramps occur under benign circumstances. Persons vary widely in their susceptibility; most experience them rarely, but the occasional subject is annoyed by frequent recurring spasms. The commonest sites are the gastrocnemius-soleus group, small muscles of foot and hand, and abductors of hip. In some persons the cramp occurs during or some minutes or hours after the close of some unusual activity or muscular effort; in many the cramp of leg

or foot appears most frequently after retiring or during sleep. Recurring paroxysms of nocturnal cramps in legs are experienced commonly during pregnancy. In each of these circumstances there is no recognized threat other than the intense discomfort; on the other hand, the swimmer or mountaineer, for example, may expose himself to a greatly increased hazard if he is susceptible to cramps.

In another group of patients, muscular cramps appear in association with general distortions of mineral metabolism owing to a wide range of underlying disturbances, some transient, others more ominous. The simplest form occurs as a result of extensive salt depletion in normal man, as in miner's cramps, or after rigorous and protracted restriction of salt in the diet. The tetany of respiratory alkalosis induced by acute hyperventilation is characterized by painful muscular cramps in hands and feet. These carpopedal spasms, when full-blown, are readily distinguishable from other forms of spontaneous cramps but in *formes frustes* may be difficult to identify. Cumulative mineral deficiencies may make cramps one of the early symptoms of renal insufficiency. Another example is seen more frequently in the patient treated for chronic cardiac insufficiency by reduced salt intake. When his precarious electrolyte economy is strained, whether by an abrupt mercurial saluresis, by an extended period of hot weather and attendant sweating, or by overtreatment with an ion-exchange resin, then muscular cramps may become severe. Hypocalcemia due to such diverse causes as hypoparathyroidism, sprue, rickets, advanced renal insufficiency, or pancreatitis, and leading to tetany, may produce muscular cramps indistinguishable at first from those due to more benign causes.

In a very small group of patients the appearance of cramps may be a sequel to disease of the nervous system. Injuries of peripheral nerves may be followed sometimes by cramping in the muscles innervated by the damaged nerve. A counterpart is observed more commonly in the cramps which appear in normal muscles called on for unusual exertion by enfeeblement of their neighbors involved in some neuromuscular disease or skeletal deformity. On rare occasions an uncomplicated acute neuronitis of the facial nerve is followed by paroxysmal facial spasm. There exist a number of clinical descriptions of odd, localized "myospasms" involving muscles innervated by various cranial and spinal nerves. Rarely, patients with amyotropic lateral sclerosis complain bitterly of cramps.

In older patients with an impoverished arterial supply to the legs, claudication may masquerade as simple muscular cramps; however, spontaneous nocturnal cramps are experienced also by these patients and, it would seem, with greater frequency than occurred in their younger years.

The older literature is replete with descriptions of special cramps associated with all sorts of occupations. It is held generally that these are neurotic in origin, and it is of some interest to note the current impression that this manifestation has become relatively rare.

The disturbance in function which triggers the cramp is not well understood; nevertheless, there are certain features of the varied circumstances in which it occurs that suggest possible underlying mechanisms. The electromyographic characteristics indicate a heightened excitability of the motor unit which fires at a high frequency under the drive of obscure stimuli. This sort of hyperexcit-

ability is reflected in the spontaneous fasciculations observed commonly in the gastrocnemii of normal persons and which occur with great frequency in muscles especially likely to cramp. In several diverse circumstances leading to cramp, the common denominator appears to be a distortion of the normal anatomy of electrolyte structure. This factor is consonant with the growing precise knowledge concerning the crucial role played by electrolyte concentrations in the maintenance in excitable tissues of a normal resistance to stimulation. What local changes in excitability of muscle might underlie the appearance of cramp in otherwise normal persons is not at all clear. Speculations concerning changes in hydrogen ion concentration, sodium, potassium, or calcium shifts, postexercise swelling of the muscle fibers, critical reductions in flow of blood during rest, and many others are interesting but unproved.

Fortunately, the obscurity surrounding the mechanism of muscular cramp has not blocked the development of semiempirical means of preventing cramp. Most persons learn themselves that sustained passive stretch of the cramped muscle may end the spasm. This maneuver suggests that there may be either a central component in cramp or that the peripheral phenomenon may be overridden by the central inhibition which develops when muscle spindles are stretched. Some find that a hot bath at bedtime seems to lessen the frequency with which they are awakened by cramp.

The Cinchona derivatives have a potent and complex effect on excitable tissues, tending to reduce excitability. Benign muscular cramp is usually prevented readily by the ingestion of 0.2 Gm. of quinine sulfate at bedtime. Both quinine and hot baths are interdicted for the pregnant woman, and it is in these patients that nocturnal cramp may become a major complaint. Happily, one competent observer has noted in a small series of patients that 250 mg. of Myanesin at bedtime was as effective as quinine, and this drug is without known specific untoward effects in the pregnant woman.

This is the meager array of facts, known or guessed, which concern a common and usually benign chronic complaint. Because of its benignity it is often considered to be insignificant by all but the person who has the cramp. Relief from nocturnal leg cramps often looms in the mind of the sufferer as being as great a boon as any offered by the most skilful of therapists.

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Book Reviews

GERIATRIC MEDICINE. Edited by Edward J. Stieglitz, M.D., Fellow, American College of Physicians, with 48 contributors. Ed. 3. Pp. 718, with 205 figures; indexed. Philadelphia, 1954, J. B. Lippincott Company. Price $15.00.

Although it is true that older persons often suffer from chronic diseases, physicians must be cognizant of the fact that aging and disease are not synonymous. The third edition of Stieglitz's *Geriatric Medicine* should be of great value in clarifying some of these issues. With chapters written by forty-eight specialists, *Geriatric Medicine* affords an insight into current theories of etiology as well as modern methods of diagnosis and treatment of many of the chronic diseases such as arteriosclerosis, hypertension, cardiovascular disease, arthritis, gout, osteoporosis, the nephropathies, cirrhosis, diabetes, chronic lung disease, and endocrine disorders. However, the book does more than this. It also gives some of the fundamental anatomic, physiologic, biochemical, and psychologic characteristics of aging people to serve as a background for the interpretation of pathologic and disease states. Thus, Stieglitz outlines, in the first chapter, the biologic, medical, and social aspects of aging man with emphasis on the concept that aging is a part of living. In this and other chapters he has written in the volume, Stieglitz points out that geriatrics should not be considered a medical specialty in the usual narrow sense. To him, geriatrics is "rather the application of understanding of the changes which come with senescence to all of the facets of medical practice." To this end, informative chapters on anatomic changes (Jean Oliver), physiologic changes (A. J. Carlson), and intellectual changes (O. J. Kaplan) open the volume. These chapters, although brief, are well written and afford excellent background information. The gradual loss of parenchymal cells and the accumulation of interstitial tissues, which Stieglitz regards as a primary factor in aging, is well illustrated in Oliver's chapter. The medical care of the normal aged is dealt with in chapters by Stieglitz and Zeman. Of particular interest is an outline of the essentials of a periodic health inventory. It is Stieglitz's belief that early diagnosis and adequate preventive measures represent the key to avoid the major incapacities of old age. To him, the period of life from 40-60 years is of primary importance in minimizing the effects of chronic disease.

The clinical chapters are organized under Disorders of Metabolism (malnutrition, diseases of the blood, diabetes mellitus, gout, dysfunction of the thyroid, gonads, and adrenals), Disorders of the Mind and the Nervous System (mental diseases, organic diseases of the brain, spinal cord, and peripheral nerves, diseases of the eye, and diseases of the ear), Disorders of the Respiratory System (upper respiratory tract and lungs), Disorders of the Circulatory System (heart, myocardial infarction, arteriosclerosis, hypertension, and veins), Disorders of the Alimentary System (mouth and teeth, esophagus and small intestine, colon, rectum and anus, and liver), Disorders of the Genito-Urinary System (gynecology, the nephritides, bladder, prostate, and urethra), and Disorders of the Skeletal System and the Integument (joints, bones, and skin). With a variety of authors, the style and manner of presentation fluctuates from chapter to chapter, but all are informative. The bibliographies are selective rather than comprehensive and an occasional key reference has been omitted.

The book is well printed in double-column format and profusely illustrated.

As a reference book, *Geriatric Medicine* should be on the shelf of every physician who sees older patients—and today this means practically every internist. Unlike many reference books which are only "looked at," this book deserves to be read.

N. W. Shock

ANNUAL REVIEW OF MEDICINE. Edited by Windsor C. Cutting, M.D., Stanford University School of Medicine. Vol. 5. Pp. 490; indexed. Stanford, California, 1954, Annual Reviews, Inc. Price $7.00.

Annual Reviews, Inc., is a nonprofit corporation which, since 1931, has devoted itself to the publication, year by year, of critical reviews designed systematically to cover the current literature in certain major fields of science. These Reviews are designed for those engaged in teaching and research whose background knowledge of the subject is already well established.

The *Annual Review of Medicine* does not attempt the review of all of medicine. Apparently the choice of the field to be covered is left to individual reviewers. A more appropriate and descriptive title might be "Annual Review of Selected Topics in Medicine."

Some of the chapters are superbly written so as to be interesting and understandable to an intelligent physician of almost any persuasion, and others are so technical as to fail almost completely of attaining the expressed goal of general interest.

The present reviewer read the volume through from cover to cover, a difficult task because of the small closely set type, the frequency of abbreviations, and the galaxy of proper names.

The scholarly and authoritative character of the reviews is of the highest order and the usefulness of the volume as a reference work beyond question.

Jawitz summarizes in an interesting and readable chapter recent developments in the realm of antimicrobial therapy.

Hollander and Janowitz review selected topics on diseases of the digestive tract including cardiospasm, esophageal varices, transpyloric prolapse of the gastric mucosa, peptic ulcer, gastrointestinal bleeding, malignant tumors of the stomach, intestinal function tests, granulomatous regional enteritis, the sprue syndrome, massive resection of the small bowel, congenital megacolon (Hirschsprung's disease), chronic ulcerative colitis, amebiasis, carcinoma of the colon and rectum, diagnostic radiology of the biliary tract, cholelithiasis, and affections of the pancreas. Diseases of the liver are omitted.

Only twelve pages are devoted by Graham and Maxwell to diseases of the cardiovascular system. Coronary arterial disease, valvular disease of the heart, congenital heart disease, rheumatic heart disease, electrocardiography, ballistocardiography, phonocardiography, peripheral vascular disease, heart failure, and hypertensive heart disease are the topics discussed. This chapter is recommended only as a source of references.

Newman and Pocock present a highly technical discussion of diseases of the kidney from the point of view of the renal physiologist. The topics include regulation of water and sodium excretion, diuretics, the kidney and hypertension, nephritides and nephropathies, and renal transplant.

Stefanini and Dameshek review certain hemorrhagic disorders, including the thrombocytopenic states, acute vascular purpura, coagulation defects, and fibrinolytic purpura.

Soffer and Gabrilove discuss the latest developments pertaining to the adenohypophysis, the neurohypophysis, the adrenals, the parathyroid glands, and the thyroid gland.

Medical care in advanced cancer is lucidly discussed by Gellhorn and Holland. Nitrogen and calcium metabolism, and anemia in the neoplastic state, radiotherapy, chemotherapy, the control of pain, and psychologic aspects are covered.

Tyler and Armstrong review the metabolic aspects of schizophrenia, phenylketonuria, progressive muscular dystrophy, multiple sclerosis, and hepatolenticular degeneration.

Heath discusses the relationship of advances in the basic sciences to an understanding of human behavior, and the new trends in the concepts of psychiatric education.

Lilienthal and Riley present an exhaustive, scholarly, and highly technical discussion of the circulation through the lung and diffusion of gases. Hemodynamics, geometric considerations, shunts and the bronchial circulation, control of the pulmonary circulation, and diffusing capacity are considered in detail.

Recent experimental work in the field of traumatic shock, including injury produced by burns, trauma, and hemorrhage, is reviewed by Millican and Rosenthal. A section on therapy is included.

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The discussion of three controversial topics in the field of anesthesia by Dripps, including the use of the curare group of drugs, controlled deliberate hypotension, and the neurologic complications of spinal anesthesia, is excellent.

Lorenz and Congdon review the processes involved in irradiation injury and its prevention, in the induction of experimental leukemia, and in the irradiation treatment of experimental tumors.

Middlebrook reviews the phenomena of hemagglutination and conditioned hemolysis in tuberculosis.

The chapter on toxicology by Smyth is unusually readable. The interests and methods of industrial toxicology and the special topics of pesticides, food additives, atmospheric pollution, inorganic chemicals, and chlorinated hydrocarbons are discussed.

The masterly critical review by Pillsbury and Shelley might well serve as a model to the editors for contributions to future editions of the *Annual Review*. Included are steroid therapy in skin diseases, antimalarial compounds in the treatment of discoid lupus, the treatment of fungus infections, diseases of the eccrine sweat glands, and urticaria pigmentosa.

A number of topics in the field of pediatrics are briefly reviewed by Wilson, including causes of congenital anomalies, antibiotics, tuberculosis, poliomyelitis, renal physiology, nephrosis, retrolental fibroplasia, pulmonary "hyaline membrane," chronic eosinophilia with hepatomegaly, megaloblastic anemia of infancy, erythroblastosis fetalis, and advances in the treatment of congenital heart disease.

Leicester discusses the etiology of dental caries.

The volume closes with an annotated list of reviews in medicine compiled by Mackay.

The *Annual Review of Medicine* renders no mean service to the insatiable problem of current literature and is recommended as a "must" for all libraries, teachers, and researchers. The bibliography of the selected topics is exhaustive.

Richard D. Hahn

OBESITY. By Edward H. Rynearson, M.D., Associate Professor of Medicine, and Clifford F. Gastineau, M.D., Fellow in Medicine, Mayo Foundation. Second printing. Pp. 144, with 9 figures, 16 tables. Springfield, 1954, Charles C Thomas, Publisher. Price $3.75.

The reprinting of this book five years after first publication is testimony of its value. Without meaning to belittle this, it may be observed that no serious competition has been offered as a simple compendium for the physician who has to treat obesity and prescribe sound reduction diets, in spite of the fact that this is increasingly called for in medical practice. Much has been learned about obesity in recent years and even in 1949 it could be objected that many questions were treated rather superficially in *Obesity*. The discussion of the psychologic aspects of obesity was obviously inadequate in 1949. Now there are important new facts about the body composition and metabolism, the etiology of obesity, and relationship to health and disease, which the practicing physician should know about. And the doctor should be able to answer his patient's questions about the many new diets and pharmaceutic preparations offered for weight reduction and well publicized in the popular press. These are reasons for disappointment in being offered a reprint instead of a new edition. But this book by Rynearson and Gastineau is still useful and it is good to maintain it in print.

Ancel Keys

MUSCULAR CONTRACTION. By M. Dubuisson, Ph.D., Director, Laboratory of General Biology, University of Liege, Belgium. Pp. 243; indexed. Springfield, 1954, Charles C Thomas, Publisher. Price $6.50.

A flabby bit of soft muscle can exert such forces as to lift more than one thousandfold its own weight, and this extraordinary feat is performed with a degree of efficiency exceeding any man-made machine. Knowledge of these facts has stimulated much thought and investigation of the various phenomena which account for the amazing properties of contractile tissue. With

each conceptual and technologic advance in this area there has followed a flood of new observations. Since the turn of the century there have been recurring floods of this kind, now chemical, now physical, now electrical in concept and means of measurement. At flood stage, the mass of fragmentary data rushes by in an almost unrecognizable jumble, but as the crest recedes, order appears out of the important facts which are left in its wake.

It seems now as though we are being swept by a major flood in respect to muscle function. Brilliant advances in the areas of chemical composition of muscle and physicochemical aspects of contraction are visible but become difficult to align because of the mass of observations which continue to swell the flood. This review by Dubuisson, himself a distinguished contributor to the field, has virtues and faults which are attributable to the state of the art. Buttressed by 764 separate references to the literature, the great majority of which appeared in the last decade, the author has collated many observations dealing with the chemistry of muscular contraction. The result is an appropriate division into "what is known about physicochemical aspects of muscular contraction, which is the dynamic part of the subject, and the properties of the muscle constituents which is a rather static side of the problem." The gap between these phases is still wide.

This monograph is a valuable compilation of considerable usefulness to specialists in the field. Its lack of unifying concepts or critique, likely to be an unavoidable result of the flood stage of investigative activity, makes the book of little use to the casual but interested reader. It seems worth while pointing out that because of the gaps existing in knowledge of the behavior of normal muscle, an understanding of what occurs in disease is hull down on the horizon.

Joseph L. Lilienthal, Jr.

HANDBOOK OF TROPICAL DERMATOLOGY AND MEDICAL MYCOLOGY. Edited by R. D. G. Ph. Simons, Senior Lecturer at the Dermatological Clinic of the University of Leyden, and Dermatologist in Charge at the Civilian Hospital, Amsterdam. Vol. 2. Pp. 1705; indexed. Houston, 1954, Elsevier Pub. Co. Price $15.00.

The editor has carefully chosen a cosmopolitan group of contributors to his second volume, which comprises diseases due to animal parasites, fungus diseases, metabolic disturbances, and tumors. Each subject has been comprehensively covered so that the book constitutes a valuable reference text. The sections on animal parasites and mycology have been handled particularly well.

The printing is clear and the illustrations are, in general, excellent. The book is recommended to the internist as well as the dermatologist, and to practitioners in temperate climates as well as students of tropical medicine.

R. C. V. Robinson

CORONARY HEART DISEASE IN YOUNG ADULTS: A MULTIDISCIPLINARY STUDY. By Menard M. Gertler, M.D., and Paul D. White, M.D., with the aid, advice, and editorial assistance of E. F. Bland, M.D., J. Fertig, Ph.D., S. M. Garn, Ph.D., J. Lerman, M.D., S. A. Levine, M.D., H. B. Sprague, M.D., and N. C. Turner, M.Sc. Pp. 218. Published for the Commonwealth Fund by Harvard University Press, Cambridge, 1954. Price $5.00.

This monograph presents the findings of a three-year investigation of coronary heart disease in young adults conducted at the Massachusetts General Hospital and the Harvard Medical School by a distinguished group of scientists under the leadership of Paul D. White and the direction of Menard M. Gertler. The study was a many-sided inquiry into the problem of what kind of an individual has a myocardial infarction at an early age in the absence of other serious chronic disorders, including hypertension, diabetes, and syphilis. By this approach it was hoped to find new information concerning the nature of coronary heart disease which might help in the recognition of persons most likely to suffer from this disorder.

One hundred persons who had sustained an attack of myocardial infarction at or before age 40 were selected; all were ambulatory, having had the acute attack at least six months before, and were from 24 to 51 years of age when examined. For comparison, two control groups were studied: a general group of 146 males of age, occupation, and ethnic origin similar to the coronary heart disease group, and a matched control group of ninety-seven males in which not only age, race, and occupation, but also height, weight, and body build, were closely equated by the matched-pair technique. Systematic examinations were carried out during a brief hospital admission; the special investigations included morphologic, genetic, athletic, occupational, physiologic, psychologic, clinical, dietary, hormonal, and biochemical aspects.

Of the 100 patients, who were 22 to 40 years of age at the time of the acute episode, only three were women. This fact again emphasizes the predominance of "pure" coronary heart disease among males in the younger age groups, a situation which is not found after middle life. Almost all the coronary patients appeared at least a decade older than their chronological ages; otherwise, no unusual clinical features were found. Studies of family incidence revealed that the parents and siblings of the coronary group had significantly more coronary heart disease than did the parents and siblings of the unmatched control group, and that more of the fathers and mothers of the coronary group than of the control group were dead. No definite hereditary pattern could be identified; the authors concluded that the disorder runs in families and is possibly a multiple-factor condition with at least one dominant factor.

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The physiques of the coronary group and of the unmatched control group were rated in various ways, with special regard for anthropometric techniques and the somatotype method of Sheldon. In general, the control group was taller and more linear than the coronary heart disease group. Whereas the coronary group was shorter, it was at the same time absolutely broader. Both the coronary and the control groups showed approximately the same degree of overweight with respect to the Army norms. There were twice as many dominant mesomorphs and only one-third as many dominant ectomorphs in the coronary heart disease group as in the control group.

Evaluation of masculine versus feminine characteristics revealed that in morphologic make-up the coronary patients were more masculine than the unmatched control group. Psychologically, however, the coronary group showed attitudes considered more typically feminine than the control group. No significant differences were found between the two groups in regard to hair graying, baldness, or distribution of body hair. Endocrine studies yielded no definitely significant information in respect to twenty-four-hour urinary sterone excretion, but a suggestive lowering of urinary keto-steroids was noted in the nine males who died from coronary heart disease within four months of the test, as compared with the male patients who survived for a longer period. Also, there appeared to be a slight alteration in thyroid activity in the direction of hypothyroidism among the coronary patients as a whole.

The remainder of the volume sets forth the dietary and biochemical findings, together with some original observations on the oxidation-reduction potentials of saliva. The level of serum total cholesterol for the coronary group was increased over the control levels, and this held true for each physique, reaching its highest value in the coronary mesomorph in contrast to the lowest value in the control ectomorph. There was no evidence that ingestion of large amounts of cholesterol in the diet influenced the level of cholesterol in the blood. The level of serum uric acid was higher in the coronary group than in the control groups, but the difference was statistically significant for only one type of physique: the endomorphic. Some differences were found in the oxidation-reduction potentials of saliva from coronary and control groups, but the basis of this phenomenon is as yet unexplained.

One of the questions which the present study cannot answer concerns the characteristics of young adults who succumb to an attack of acute myocardial infarction. Its importance was emphasized by the studies of coronary artery disease in men 18 to 39 years of age carried out by Yater and his associates. Of the 866 cases of acute myocardial infarction in young soldiers reported by them, less than one-half recovered. Since the present study includes only persons who survived such an attack for at least six months, information is lacking as to whether the traits here described as typical of the *living* coronary heart disease patient would be present to

an equal extent among young coronary victims who died. In the latter group, the findings might be *more* pronounced, but they might, surprisingly, be *less* marked. Indeed, certain different and possibly crucial determinants might come to light among them which would provide a special warning of disaster.

The book has many excellent graphs and tables, as well as a series of photographs illustrating the variety of somatotype ratings found in the coronary heart disease group. Altogether, this is a stimulating and thought-provoking contribution to the rapidly growing literature regarding the etiology of coronary heart disease. It should be read not only by all who are concerned with the various aspects of that difficult problem, but also by clinical investigators in allied fields.

Caroline B. Thomas

PHYSIOLOGY AND BIOCHEMISTRY OF THE SKIN. By Stephen Rothman, M.D., Professor of Dermatology, University of Chicago. Pp. 741; indexed. Chicago, 1954, University of Chicago Press. Price $19.50.

This is a great book. It has the greatness of authorship by a man who has international eminence in both dermatology and physiology. It has the greatness of its subject, basic research in dermatology. And, finally, it has the greatness of an approach which is encyclopedic, thoughtful, and stimulating.

No one has contributed more to the founding of the discipline "cutaneous physiology" than Professor Rothman. A graduate of the University of Budapest in 1917, Rothman had a distinguished career in Europe in the fields of both clinical and research dermatology. His monumental review of the biochemistry of skin was published in 1929 as part of the famous Jadassohn *Handbuch fur Haut-krankheiten*. In 1935 he was Secretary-General of the Ninth International Congress of Dermatology held in Budapest. Since 1938 he has been at the University of Chicago, where his research activities have continued to enliven nearly every phase of dermatologic physiology and chemistry.

All this has been in addition to his active role in the advancement of clinical dermatology. As would be expected from a man who has so successfully integrated the clinical and experimental, Rothman has written a book which presents the physiologic basis for understanding both the normal and the abnormal functions of the skin.

Strangely, cutaneous physiology is a recently explored field. Early physiologists so sharply limited their efforts to the problems of circulation, respiration, and digestion that even today tradition and interest have maintained these as the primary respectable fields of endeavor. The problems of the skin were touched only tangentially by medical physiologists. The major questions posed by clinical dermatologists remained unstudied and unanswered. Even today not a single textbook of physiology gives an account of itching, one of the most common sensations and symptoms known to the patient. It became apparent that research in the physiology of the skin would have to arise largely in the clinical groups. Men such as Sir Thomas Lewis (consider his classic, *The Blood Vessels of the Human Skin*) initiated the clinicophysiologic approach, and today many dermatologic departments have research teams and individuals attacking the basic problems of the physiology of human skin. Their contributions linked with the by-products of basic science departmental endeavor have all added up to a magnificent, yet formerly untold, story of the functions of the skin. Rothman has told this story well.

He stresses the unique properties of skin. He has not written a textbook of physiology with a dermatologic slant. Rather he has produced a comprehensive interpretative summary of the world's knowledge of the physiology of the skin itself. His book gives impact and substance to what was previously scattered beyond the reach of both index and investigator. Although Comel in 1933 wrote a mammoth two-volume work in Italian, no previous compilation was ever achieved in English.

In Rothman's work, after a brief introduction to the biophysical properties of skin, one reads an engrossing account of the passage of materials across this cutaneous membrane. The details of the permeability and impermeability of skin are recounted with emphasis on the skin appendages, the substance, and the vehicle. The problems of skin circulation and vascular reaction are

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treated next. This is followed by a detailed account of pruritus and pain. The apocrine, eccrine, and sebaceous glands of the skin are carefully reviewed both from the chemical as well as the physiologic standpoint.

In the second half of the volume the epidermal functions of keratinization and melanin formation are subjected to precise analysis. The latter section is ably written by one of Professor Rothman's distinguished contributors, Allan L. Lorincz. Five other contributors each wrote an authoritative chapter:

Zachary Felsher—Collagen, Reticulin, and Elastin,
George C. Wells—Ground Substance,
Aaron B. Lerner—Enzymes,
Hermann Pinkus—Biology of Epidermal Cells,
Peter Flesch—Hair.

The remainder of the book is concerned with the metabolism of the skin, with separate sections on proteins, lipids, carbohydrates, and electrolytes. Finally, strictly clinical problems of nutrition, blister formation, and sweat retention are viewed from the physiologic vantage point.

Rothman's treatment is comprehensive and scholarly. His critical interpretative accounts present the subject in its entirety. This book must stand as the solitary reference source for all of modern dermatophysiology. In its twenty-eight chapters it lists by full title, 3,674 selected references, which immediately bring the reader into contact with the rich heritage which is his.

Rothman brilliantly employs the historical perspective to orient his readers. The origins of knowledge are as clearly depicted as the present extensions. The currency of reference is at times astonishing when one considers the great time lag generally appearing in even periodical publications.

Methods are mentioned but never described in detail. This is a book devoted to basic unifying concepts, and Rothman has both crystallized as well as criticized many of these throughout the work. Frequently, promising research vistas of the future are presented the reader. Nowhere has Rothman failed to bring his dynamic personality into evidence. Mere facts are never simply recorded without any indication of their relationship to the total topic. Throughout, the organization is superb. This book should prove of incalculable worth to both the investigator and the physician interested in skin.

Technically the book is excellent. The typography and photographs are of good quality. Nearly 300 graphs, tables, and illustrations add to the reader's comprehension. Both an author and subject index are appended. The large page size has resulted in a book much larger than 741 pages might suggest.

In summary, Rothman's book establishes a new specialty—cutaneous physiology. Long may it flourish!

Walter B. Shelley

Books Received

DONOVANOSIS (Granuloma Inguinale, Granuloma Venereum). By R. V. Rajam, M.S., F.R.C.P., and P. N. Rangiah, M.D. Pp. 72; indexed. Geneva, 1954, World Health Organization. Price $1.50.

TREPONEMATOSES. A World Problem. By T. Guthe, M.D., M.P.H., and R. R. Willcox, M.D. Pp. 79; indexed. Geneva, 1954, World Health Organization. Price $0.50.

ATLAS OF HUMAN ANATOMY. By Franz Frohse, Max Brodel, and Leon Schlossberg. Pp. 88; indexed. New York, 1953, Barnes & Noble, Inc. Price $2.00.

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